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Hypersensitivity Reactions to Iodinated Contrast Media

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SAŽETAK: Jodni kontrastni mediji uporabljuju se pri rentgenskim postupcima te mogu izazvati neposredne i odgođene reakcije preosjetljivosti. Zbog njihove povećane primjene, reakcije preosjetljivosti također su u porastu. Nakon uvođenja neionskih, niskoosmolarnih kontrastnih medija, smanjio se broj reakcija preosjetljivosti, no moguće teške reakcije, kao što je anafilaksija, i dalje su ozbiljan problem. Radiolozi i kardiolozi trebaju imati na umu da dosad neizloženi pacijenti mogu već imati razvijenu osjetljivost te mogu pokazati reakciju preosjetljivosti nakon prve primjene kontrastnog medija. U pacijenata koji su već imali reakciju (tj. u prijašnjih reaktora), pogotovo kad su bile posrijedi teške reakcije, alergološka obrada može pomoći pri izboru prikladnoga kontrastnog medija. U pacijenata s potvrđenom alergijom na kontrastne medije treba se koristiti kontrastnim medijem koji je imao negativan kožni test, uz dodatne premedikacije. Ipak, treba imati na umu da ove mjere ne mogu u potpunosti osigurati sprečavanje ponovljene reakcije.

SUMMARY: Iodinated contrast agents are used to enhance X-ray procedures and can cause both immediate and non-immediate hypersensitivity reactions. Due to their increased use, related hypersensitivity reactions are also on the rise. Following the introduction of nonionic, low-osmolar contrast media the number of hypersensitivity reactions has decreased, but possible severe reactions, such as anaphylaxis, still represent a major concern. Radiologists and cardiologists should keep in mind that previously non-exposed patients could already be sensitized, and could present with a hypersensitivity reaction following the first administration. In previous reactors, especially in cases of severe reactions, an allergy work-up could provide useful information regarding contrast media selection. In patients with a confirmed allergy to contrast media, a contrast medium that has a negative skin test should be chosen, with additional premedication. However, we must keep in mind that none of these measures offer a complete protection from repeated reaction.

KLJUČNE RIJEČI: neželjena reakcija, jodni kontrastni mediji, premedikacija.

KEYWORDS: adverse reaction, iodinated contrast media, premedication.

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Uvod

Jodni kontrastni agensi koncentrirane su otopine jodnih benzenskih derivata koji se rabe pri rentgenskim postupcima[1]. Ti se agensi općenito smatraju sigurnima, no mogu uzrokovati neposredne (< 1 sat nakon primjene) ili odgođene (> 1 sat nakon primjene) reakcije preosjetljivosti. Neželjene reakcije koje mogu nastupiti nakon primjene kontrastnih medija mogu biti alergijske i nealergijske reakcije preosjetljivosti, toksične reakcije te reakcije nevezane za izloženost kontrastnim medijima[2]. Jodni radiokontrastni mediji

Introduction

Iodinated contrast agents are concentrated solutions of iodinated benzene derivatives used to enhance X-ray procedures[1]. These agents are generally considered safe but can cause both immediate (<1 hour after treatment) and non-immediate (>1 hour after treatment) hypersensitivity reactions. Adverse reactions following the administration of contrast media are usually divided into allergic and non-allergic hypersensitivity reactions, toxic reaction and reactions that are not related to contrast media exposure[2].

primjenjuju se diljem svijeta više od 75 milijuna puta godišnje[3], a zbog njihove povećane primjene reakcije preosjetljivosti također su u porastu.

Jodni se kontrastni mediji dijele u četiri klase: ionski i neionski monomeri te ionski i neionski dimeri. Ionski kontrastni agensi s višom osmolalnosti češće uzrokuju neželjene reakcije u usporedbi s neionskim kontrastnim agensima niže osmolalnosti, pa je potonje stoga preporučljivo rabiti u pacijenata s povećanim rizikom od neželjenih reakcija, prema Američkom koledžu za radiologiju. No i novije generacije kontrastnih medija mogu uzrokovati neposredne i odgođene reakcije u 1 do 3 % primjena[4]. Broj se reakcija preosjetljivosti na kontrastne medije smanjio nakon uvođenja neionskih, niskoosmolarnih kontrastnih medija, no moguće teške reakcije opasne za život, kao što je anafilaksija, i dalje su ozbiljna briga za liječnike i pacijente.

Klinički podatci i čimbenici rizika

Većina reakcija preosjetljivosti nastupa nakon intravenske primjene kontrastnog medija, najčešće unutar prvog sata od primjene[5,6]. Najzastupljenije su manifestacije neposrednih reakcija svrbež i osip, koji se pojavljuju u oko 70 % pacijenata[4,5]. U težim slučajevima mogu biti zahvaćeni respiratorni i srčanožilni sustav, uz zaduhu, bronhospazam, laringealni edem, hipotenziju, tahikardiju i aritmiju i šok. Nakon primjene kontrastnih medija moguća je i smrtonosna anafilaktična reakcija[4,7,8]. Anafilaktične su reakcije teške, sustavne reakcije preosjetljivosti opasne za život, koje pri prvom izlaganju kontrastnim medijima mogu nastupiti u 30 do 35% slučajeva. Prethodna preosjetljivost na kontrastne medije najvažniji je čimbenik rizika i za neposredne i za odgođene reakcije preosjetljivosti. Pacijenti koji su već imali reakciju imaju rizik od 21 do 60 % da će pri ponovljenoj primjeni istog ili sličnog ionskoga kontrastnog medija ponovno doći do reakcije[4,9,10]. Ostali poznati čimbenici rizika za teške reakcije preosjetljivosti uključuju astmu ili druge ozbiljne alergije koje trebaju sustavno liječenje, terapiju beta-blokatorima, bolesti srca, ženski spol, maligne tumore, mediteranski i indijski etnicitet te čak i anamnestički podatak o alergiji na morske plodove[7,9,11]. Zamjena ionskoga kontrastnog medija neionskim kod prijašnjih je reaktora dovela do čak 10 puta manje incidencije teških ponovljenih reakcija[10].

Odgođene se reakcije najčešće pojavljuju unutar 48 sati te se manifestiraju kožnim erupcijama u obliku osipa, najčešće makulopapularnim osipom[5,12,13]. Ostale česte odgođene reakcije uključuju eritrem, makularni egzantem, urtikariju te angioedem[14,15]. Odgođene su reakcije općenito blage, prolazne i samoograničavajuće, no povremeno mogu nastati ozbiljnije kožnih reakcija kao što su kožni vaskulitis, reakcija na lijek s eozinofilijom, Stevens-Johnsonov sindrom ili toksične epidermalne nekrolize[15]. Među čimbenicima rizika za odgođene reakcije jesu prethodna neželjena reakcija na kontrastni medij, liječenje interleukinom-2, povišena razina kreatinina u serumu > 2,0 mg/dL i anamnestički podatak o kontaktnim i alergijama na lijekove[12,16]. Smatra se da prisutnost mastocitoze, autoimunosnih bolesti i virusnih infekcija pri primjeni

More than 75 million iodine-based radiocontrast media are used worldwide every year[3], and due to their increased use, related hypersensitivity reactions are also on the rise.

Iodinated contrast media are divided into four classes: ionic and non-ionic monomers, and ionic and non-ionic dimers. Ionic contrast agents with higher osmolality more commonly cause adverse reactions than low osmolality non-ionic contrast agents, and the latter have thus been recommended by The American College of Radiology for patients with increased risk of adverse reactions. However, even newer generations of contrast media can cause immediate and non-immediate reactions in an average of 1% to 3% of applications[4]. Following the introduction of nonionic, low-osmolar contrast media, the number of hypersensitivity reactions to contrast media has decreased. Possible occurrence of life-threatening, severe reactions, such as anaphylaxis, still represents a major concern for physicians and patients.

Clinical findings and risk factors

The majority of hypersensitivity reactions occur following intravenous administration of contrast media and are immediate reactions occurring within the first hour[5,6]. The most common manifestation of immediate reaction is pruritus and urticaria, occurring in around 70% of patients[4,5]. In more severe cases, the respiratory and cardiovascular system could be involved, with dyspnea, bronchospasm, laryngeal edema, hypotension, tachycardia and arrhythmia, and shock. Finally, a possibly fatal anaphylactic reaction could occur following contrast media administration[4,7,8]. Anaphylactic reactions are a life-threatening, severe, systemic hypersensitivity reaction that can occur at the first exposure to contrast media in 30-35% of cases. The most important risk factor for developing both immediate and non-immediate adverse reactions is previous hypersensitivity reaction to contrast media. Previous reactors have a 21-60% risk of a repeated reaction following re-exposure to the same or similar ionic contrast media[4,9,10]. Other known risk factors for developing severe hypersensitivity reactions include asthma or other serious allergies requiring systemic treatment, treatment with beta-blockers, cardiac disease, female sex, malignant tumors, Mediterranean and Indian ethnicity, and even history of seafood allergy[7,9,11]. Switching from an ionic contrast to non-ionic contrast media in previous reactors resulted in a 10-fold reduction of the incidence of severe repeat reactions[10].

The non-immediate reactions generally appear within 48 hours and are usually manifested as exanthematous skin eruptions, most commonly maculopapular rash[5,12,13]. Other frequent non-immediate reactions include erythema, macular exanthema, urticaria, and angioedema[14,15]. Generally, non-immediate reactions are mild, transient, and self-limiting, but occasionally severe skin reactions can occur, such as cutaneous vasculitis, drug reactions with eosinophilia, Stevens-Johnson syndrome, or toxic epidermal necrolysis[15]. Some risk factors for non-immediate reactions include a previous contrast media adverse reaction, interleukin-2 therapy, increased serum creatinine level >2.0 mg/dL, and history of contact and drug allergy[12,16]. It has been suggested that mastocitosis, auto-

kontrastnog medija mogu utjecati na težinu reakcije preosjetljivosti[17,18].

Dijagnoza

Reakcije preosjetljivosti na kontrastne medije obično su se svrstavale u nealergijske reakcije[2]. Nedavna multicentrična prospektivna studija pokazala je da je barem 50 % reakcija preosjetljivosti nakon primjene kontrastnih medija uzrokovano imunološkim mehanizmima[5]. Prethodna su istraživanja pronašla različite razine osjetljivosti na intradermalni kožni test, od 4,2 % kod pacijenata s preosjetljivosti na kontrastne medije[19] do oko 50 % u Francuskoj studiji[15] te 57,1 % u slučajevima teških neposrednih reakcija[20]. Učestalost pozitivnih kožnih testova s vremenom se znatno smanjuje zbog gubitka osjetljivosti, osobito u slučajevima neposredne reakcije[5]. U većine pacijenata s neposrednim reakcijama nije nađena alergija posredovana imunoglobulinom E pa uzročni mehanizam i dalje nije poznat.

Ubodni i intradermalni kožni testovi provode se za dijagnosticiranje neposredne alergije na kontrastne medije te su se pokazali korisnima u otkrivanju uzročnika u slučajevima neposrednih reakcija, ali i u nekim slučajevima odgođenih reakcija. Ti testovi također imaju važnu ulogu pri izboru sigurnoga kontrastnoga sredstva u prijašnjih reaktora[5,21,22]. Provokacijski test važan je i učinkovit pri otkrivanju visokorizičnih pacijenata, no vremenski je zahtjevan i potencijalno opasan za pacijenta. Tijekom *in vivo* testiranja neki su istraživači otkrili određena IgE protutijela specifična za kontrastne medije, no njihova je prisutnost bila u rasponu od 2 do 3 %[23] do 47 %[24] u pacijenata s neposrednom reakcijom. Potencijalnu ulogu *in vitro* testa neposrednog oslobađanja histamina ili drugih *in vitro* testova aktivacije bazofila u dijagnosticiranju alergije na kontrastne medije tek treba utvrditi, no prethodne su studije pokazale povećano otpuštanje histamina u prijašnjih reaktora u usporedbi sa zdravim dobrovoljcima[25].

Pri odgođenim se reakcijama smatra da je preosjetljivost posredovana limfocitima T mehanizam koji uzrokuje reakciju, što potvrđuju često pozitivni epikutani i odgođeni intradermalni testovi u prijašnjih reaktora[26-28] te ponovno stvaranje erupcija nakon testa ponovne stimulacije[29]. U nekim se slučajevima odgođene preosjetljivosti primjenjivao test transformacije limfocita[27], no taj test nije preporučljiv za redovitu uporabu. Drugi *in vitro* testovi uključuju protočnu citometriju, kulture limfocita, stanične linije i hibridome[30].

Premedikacija i biranje kontrastnog medija

U pacijenata s čimbenicima rizika ili prethodnom neželjenom reakcijom najčešće se upotrebljavaju niskoosmolarni neionski kontrastni mediji zbog niže incidencije reakcija preosjetljivosti[31,32]. Ako treba ponovno izložiti pacijenta s prethodnom neželjenom reakcijom na pojedinačni kontrastni medij, potrebno je izabrati kontrastni medij koji je negativan u kožnom testu. Zbog križne reaktivnosti između različitih kontrastnih medija do reakcije preosjetljivosti može doći čak i ako se promijeni kontrastni medij. Preporučljivo je izbjegavati izlaganje kontrastnom mediju u pacijenata s prijašnjom teškom

immune diseases, and viral infection at time of administration of contrast media could influence the severity of a hypersensitivity reaction[17,18].

Diagnosis

Contrast media hypersensitivity reactions have usually been classified as non-allergic reactions[2]. A recent prospective multicenter study suggested that at least 50% of hypersensitivity reactions following the administration of contrast media are due to immunological mechanisms[5]. Previous studies reported variable sensitivity of the intradermal skin test, from 4.2% among patients with contrast media hypersensitivity[19] to about 50% in a French study[15], and up to 57.1% in severe immediate reactions[20]. The frequency of positive tests significantly decreases with time due to loss of sensitization over time, especially in cases of immediate reactions5. In the majority of immediate reactors, immunoglobulin E -mediated allergy had not been detected so the underlying mechanism remained unknown.

Skin tests, both prick and intradermal, are performed in the diagnosis of immediate allergy to contrast media and have been shown to be useful in identifying the causative agent in cases of immediate reaction, as well as in some cases of non-immediate reaction. They also play an important role in the selection of a safe contrast media in previous reactors[5,21,22]. A provocation or challenge test is important and effective in identifying high-risk patients, but time consuming and potentially threatening for the patient. During in vivo testing, certain contrast media specific IgE antibodies were detected by some investigators, but the presence varied greatly from 2-3%[23] to 47%[24] in immediate reactors. The potential role of in vitro direct histamine release tests and other in vitro basophil activation tests in the diagnosis of contrast media allergy remains to be determined, although previous studies have shown increased histamine release in previous reactors as compared with healthy volunteers[25].

In non-immediate reactions, T cell mediated hypersensitivity is considered to be the mechanism causing the reaction, as confirmed by frequently positive patch skin tests and delayed intradermal tests in previous reactors[26-28] as well as the reappearance of the eruption after challenge testing[29]. In some cases of non-immediate hypersensitivity, a lymphocyte transformation test was used[27] but it is not recommended for routine usage. Other in vitro tests include flow cytometry, lymphocyte cultures, cell lines, and hybridomas[30].

Premedication and contrast media selection

In patients with risk factors or a previous adverse reaction, low-osmolar non-ionic contrast media are generally used due to lower incidence of hypersensitivity reactions[31,32]. In patients with a previous adverse reaction to a certain type of contrast media, a contrast medium that is skin test negative should be chosen if re-exposure is required. Due to cross-reactivity between different contrast media, hypersensitivity reactions can occur even if the contrast medium is changed. It is advisable to avoid contrast media re-exposure in patients

neposrednom reakcijom izazvanom kontrastnim medijem, kao što je anafilaksija. U takvim se slučajevima mogu rabiti alternativni kontrastni agense kao što su ugljikov dioksid i gadolinij[33].

Primjena premedikacije u prijašnjih reaktora i rizičnih pacijenata uobičajena je praksa, no treba imati na umu da se mogu razviti reakcije proboja[34]. Prethodna reakcija u pacijenta povezana je s povećanim rizikom od nove reakcije nakon ponovnog izlaganja kontrastnim medijima, a premedikacija, koliko se čini, smanjuje simptome u prijašnjih reaktora. U pacijenata s umjerenom do teškom prijašnjom reakcijom često se primjenjuje premedikacija s kortikosteroidima samostalno ili u kombinaciji s antihistaminicima i drugim lijekovima[30,34]. Jedan je pregledni članak upozorio na to da je većina neselekcioniranih pacijenta trebala dvostruku oralnu dozu metilprednizolona kako bi se izbjegle neželjene reakcije na kontrastne medije potencijalno opasne za život[34]. Nažalost, i dalje nema podataka koji bi potkrijepili učinkovitost primjene premedikacije u rizičnih bolesnika[34].

Rasprava

Radiolozi i kardiolozi trebaju imati na umu da je barem 50 % reakcija preosjetljivosti na kontrastne medije uzrokovano imunosnim mehanizmima. Pokazano je da je 30 % pacijenata s pozitivnim kožnim testovima prvi put primalo kontrastne medije, što upućuje na to da i neizloženi pacijenti mogu već razviti osjetljivost i imati reakciju preosjetljivosti pri prvoj primjeni medija[5,21].

U prijašnjih reaktora, pogotovo u slučaju teških reakcija, alergološka obrada može pružiti korisne podatke pri izboru kontrastnog medija[5]. Kožni su se testovi pokazali dobrim alatom za dijagnosticiranje alergija na kontrastne medije i pri biranju sigurnoga proizvoda u bolesnika u kojih se već razvila osjetljivost. Kod pacijenata s potvrđenom alergijom na kontrastne medije treba se koristiti kontrastnim medijem koji je bio negativan na kožnom testu te premedikacijom. Ipak, samo mali udio pacijenata s teškim reakcijama na kontrastne medije imaju pozitivan kožni test pa stoga treba imati na umu da nijedna od ovih mjera ne štiti u potpunosti od ponovne reakcije. Liječnici koji rade s kontrastnim medijima ne bi se trebali isključivo oslanjati na premedikaciju, nego trebaju biti podučeni za prepoznavanje i liječenje neželjenih reakcija ako one nastupe.

with previous severe immediate reaction induced by contrast media, such as anaphylaxis. In such cases, alternative contrast agents such as carbon dioxide and gadolinium could be used[33].

Use of premedication in previous reactors and patients at risk is a common practice, but one must keep in mind that breakthrough reactions could develop[34]. Previous reactors have been associated with increased risk of new reaction following re-exposure to contrast media, and premedication appears to reduce symptoms in previous reactors. In patients with a previous moderate to severe immediate reaction, premedication with corticosteroids alone or in combination with antihistamines and other drugs is commonly used[30,34]. A systematic review suggested that the majority of unselected patients required an oral double dose of methylprednisolone to prevent a potentially life threatening adverse reaction to contrast media[34]. Unfortunately, data supporting the efficacy of premedication administration in at-risk patients are still lacking[34].

Discussion

Radiologists and cardiologists should keep in mind that at least 50% of hypersensitivity reactions to contrast media are due to an immunological mechanism. It has been shown that 30% of patients with positive skin tests had been administered contrast media for the first time, indicating that previously non-exposed patients could already be sensitized and could present with hypersensitivity reactions following the first administration[5,21].

In previous reactors, especially in cases of severe reactions, an allergy work-up could provide useful information regarding contrast media selection[5]. Skin testing has been shown to be a good tool for diagnosing contrast media allergy and in selecting a safe product in previously sensitized patients. In patients with a confirmed allergy to contrast media, a contrast medium that is skin test negative should be chosen in association with premedication. However, as mentioned earlier, only a fraction of patients with severe adverse reactions to contrast media have a positive skin test, so one must keep in mind that none of these measures offer complete protection from a repeat reaction. Physicians working with contrast media should not rely only on the efficacy of premedication but should be trained to recognize and treat severe adverse reactions if these appear.

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