



Review

Treatment of Kounis syndrome

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ARTICLE INFO

Article history:

Received 3 February 2010

Accepted 14 February 2010

Available online 4 March 2010

Keywords:

Kounis syndrome

Allergy

Acute coronary syndrome

ABSTRACT

Kounis syndrome is potentially a life-threatening medical emergency with both a severe allergic reaction and acute coronary syndrome. Most of the information about this syndrome has come from the case reports. The management of these patients may be challenging for clinicians, and unfortunately guidelines have not been established yet. In this article, we review the current guidelines of acute coronary syndromes and anaphylaxis along with the published cases with Kounis syndrome secondary to beta-lactam antibiotics. We have summarized our recommendations for the work-up and treatment of Kounis syndrome from available data. Obviously, larger prospective studies are needed to establish definitive treatment guidelines for these patients.

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1. Introduction

The acute onset of chest pain accompanied by allergic symptoms should raise suspicion for the possibility of Kounis syndrome. This is not a simple situation, and the diagnosis and management may be challenging since the evaluation and treatment need to consider both cardiac and allergic syndromes simultaneously. The initial cardiac studies include the routine diagnostic tests for patients with acute coronary syndromes (ECG and cardiac enzymes). The allergy work-up includes assays for serum histamine, tryptase, IgE antibody, and complement proteins (C4 and C1-esterase inhibitor levels) and eosinophil counts. Elevated serum histamine and tryptase levels strongly support the possibility of an ongoing allergic reaction, but these molecules have very short half lives (less than 10 min for histamine and 90 min for tryptase) that make them (especially histamine) relatively impractical for routine use. A normal tryptase level does not exclude this possibility. Eventually these patients will need cardiac catheterization to assess the coronary anatomy, to possibly relieve vasospasm directly with intracoronary agents, and to perform angioplasty when needed. Patients with a clinical suspicion of type 2 Kounis syndrome should also have intracoronary ultrasound to identify occult coronary artery disease. This is important since the detection of nonobstructive coronary plaques would necessitate long term treatment with plaque stabilizing drugs, such as statins and antiplatelet drugs. During the follow-up, patients may need additional allergy work-up, including skin prick tests.

2. Management

2.1. Management of acute coronary syndrome

Based on the current ACC/AHA guidelines on acute coronary syndromes, the common medications are discussed individually for their therapeutic benefits and risks in patients with Kounis syndrome [1].

2.1.1. Aspirin

Aspirin should be administered to all patients with acute coronary syndrome as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant of that medication (Class I Recommendation, Level of Evidence: A). Clopidogrel (a loading dose followed by a daily maintenance dose) should be administered to patients who cannot take aspirin because of hypersensitivity or major gastrointestinal intolerance.

Although aspirin has important anti-platelet and anti-inflammatory effects in patients with coronary artery disease and acute coronary syndromes, it may cause allergic reactions and induce anaphylaxis. Aspirin and NSAIDs are two of the most frequent causes of drug associated anaphylactic reactions. This is usually mediated by IgE-sensitization and responds to intravenous antihistamines given at the onset of symptoms [2]. In addition, aspirin may influence the pathogenesis of anaphylaxis through the inhibition of cyclooxygenase. Aspirin therapy inhibits the production of prostaglandin D which would reduce one of the mediators of anaphylaxis. However, acute therapy would not necessarily reduce the synthesis of prostaglandin D following mast cell activation, but it might shunt arachidonic acid into the leukotriene pathway which produces more leukotriene C4, D4, and E4, which are important mediators of anaphylaxis. Therefore, the utility of aspirin in patients with Kounis syndrome is unknown given the potential risk of aggravating an ongoing anaphylactic reaction and the demonstrated

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benefits in acute coronary syndromes. If the clinical judgment favors the use of aspirin in these patients, it seems reasonable to give it in an intensive care unit setting with a central venous catheter in place after the initial treatment for Kounis syndrome has been started. Full resuscitation equipment and epinephrine should be available, and these patients should be monitored more closely for at least 4 h for the development of increased symptoms [2]. Aspirin desensitization could be considered later for these subjects if they have an allergy to these drugs and have a type 2 Kounis syndrome.

2.1.2. Nitroglycerin

Nitroglycerin increases myocardial oxygen delivery, vasodilates both peripheral and coronary vasculature, and decreases myocardial preload. Patients with acute coronary syndromes with ongoing ischemic pain should receive sublingual nitroglycerin (0.4 mg) every 5 min for a total of three doses, after which assessment should be made about the need for intravenous nitroglycerin, if not contraindicated (Class I Recommendation, Level of Evidence: C). Intravenous nitroglycerin is indicated in the first 48 h after an acute coronary syndrome for treatment of persistent ischemia, heart failure, or hypertension (Class I Recommendation, Level of Evidence: B). According to the current guidelines, nitrates should not be administered to acute coronary syndrome patients with systolic blood pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (less than 50 bpm), or tachycardia (more than 100 bpm) in the absence of symptomatic heart failure or right ventricular infarction (Class III recommendation, Level of Evidence: C).

Nitroglycerin causes hypotension and tachycardia which may further complicate anaphylactic reaction. In addition, although uncommon, allergic reactions to nitroglycerin do occur. Most allergic reactions to nitrates include contact dermatitis and urticaria and originate from transdermal use of nitroglycerin. Most patients with these reactions have tolerated oral and sublingual nitroglycerin [3]. Therefore, the use of intravenous or sublingual nitroglycerin seems reasonable and safe in patients with Kounis syndrome if the blood pressure is satisfactory.

2.1.3. Heparin

Heparin accelerates the action of circulating antithrombin and prevents thrombus propagation. Anticoagulant therapy should be added to anti-platelet therapy in patients with acute coronary syndromes as soon as possible after presentation (Class I Recommendation, Level of Evidence: A). Heparin is recommended to be continued for 48 h, for the duration of hospitalization, or up to 8 days and then anticoagulant therapy can be discontinued (Class I Recommendation, Level of Evidence: A).

Heparin is derived from mucosal tissues of slaughtered animals such as porcine intestine. Both unfractionated and low-molecular weight heparins can cause allergic reactions. The Center for Disease Control and Prevention has reported heparin allergy cases in hemodialysis patients at dialysis facilities [4]. Most cases resolved with treatment of H1-blockers or corticosteroids, and only four people died among 350 allergic reactions identified after receiving heparin. Most of these reactions occurred with heparin manufactured by Baxter (Baxter Healthcare Corporation, Deerfield, IL), and most of these reactions were associated with bolus heparin. Therefore, United States Food and Drug Administration recommended infusions without using a bolus dose whenever possible if a Baxter product is the only one available. These recommendations seem reasonable to follow in patients with Kounis syndrome. We suggest using a heparin product from another manufacturer or an alternative anticoagulant such as low-molecular weight heparins or bivalirudin which has been used safely in a patient with heparin allergy [5]. If a Baxter product is the only available heparin, the clinician should use a low dose at a slow infusion rate. A heparin bolus should be avoided, and the patient should be closely monitored for adverse events.

2.1.4. Beta-blockers

Beta-blockers block the effect of catecholamines on cell membrane beta-receptors. Oral beta-blocker therapy should be initiated within the first 24 h for patients who do not have one or more of the following: 1) signs of heart failure, 2) evidence of a low-output state, 3) increased risk for cardiogenic shock, or 4) other relative contraindications to beta blockade (PR interval greater than 0.24 s, second or third degree heart block, uncontrolled asthma, or reactive airway disease) (Class I Recommendation, Level of Evidence: B).

Although the use of beta-blockers is extremely beneficial in the treatment of acute coronary syndromes, these drugs may offset some of the beneficial effects of epinephrine which is the mainstay of treatment of anaphylaxis. Therefore, this decision is a complex challenge for the clinician. Glucagon may be used in patients with anaphylaxis and hypotension who are already on beta-blockers or received them during the management of the acute coronary syndrome. The dose is 1–5 mg (20–30 µg/kg; maximum 1 mg in children) intravenously as a bolus over 5 min followed by 5–15 µg/min drip, when β-blocker therapy complicates treatment.

2.1.5. Calcium-channel blockers

In patients with acute coronary syndromes and continuing or frequently recurring ischemia and in whom beta-blockers are contraindicated, a nondihydropyridine calcium channel blocker (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant left ventricular dysfunction or other contraindications (Class I Recommendation, Level of Evidence: B). Coronary spasm is very responsive to nitrates and calcium channel blockers, which are potentially first line therapy when coronary spasm is the underlying cause of chest pain such as in patients with variant angina.

Most of the allergic reactions to calcium channel blockers are minor, such as skin rash. Angioedema is extremely uncommon (eight case reports including verapamil, diltiazem, nifedipine, and amlodipine since 1950). These drugs may be also useful for the treatment of hypersensitivity induced bronchospasm. Although calcium channel blockers are not the first line of therapy in acute coronary syndromes, they may be considered the initial anti-ischemic drug of choice in patients with Kounis syndrome.

2.1.6. Morphine

Morphine has potent analgesic and anxiolytic effects. In the absence of contradictions to its use, patients should receive morphine sulfate intravenously if there is uncontrolled ischemic chest pain despite nitroglycerin, and additional therapy is used to manage the underlying ischemia (Class IIa Recommendation, Level of Evidence: B).

Opiate medications, like morphine, codeine and meperidine, should be used cautiously in this group of patients since these opiates can induce mast cell degranulation and aggravate the allergic reaction. Fentanyl and its derivatives show only a slight activation of mast cells and may be the drugs of choice when narcotic analgesia is necessary.

2.1.7. Oxygen administration

Supplemental oxygen should be administered to patients with acute coronary syndromes with an arterial saturation less than 90%, respiratory distress, or other high risk features for hypoxemia (Class I Recommendation, Level of Evidence: B). The guidelines suggest administering supplemental oxygen to all patients with acute coronary syndrome during the first 6 h after presentation (Class II recommendation, Level of Evidence: C).

In patients with anaphylactic shock, 100% oxygen administration and airway support as needed are crucial (strength of recommendation: D). Therefore, we recommend oxygen supplementation in patients with Kounis syndrome as a first line of therapy.

2.2. Management of anaphylaxis

The American Academy of Allergy Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology have provided joint practice guidelines for the diagnosis and management of anaphylaxis [6]. We review these recommendations and discuss benefits and potential hazards in patients with acute coronary syndromes.

2.2.1. H-1 blockers

Antihistamines, both H1 and H2 receptor blockers, provide symptomatic control of itching, hives, and angioedema. In general, they are considered “supportive” and “second-line treatment after administration of epinephrine” and should never be administered alone in the treatment of anaphylaxis. Specifically, diphenhydramine (1 to 2 mg/kg or 25 to 50 mg per dose) is recommended parenterally. Bolus administration of antihistamines can precipitate hypotension and compromise coronary flow; therefore, these drugs should be given slowly.

Diphenhydramine significantly affects metoprolol pharmacokinetics which results in potentially important pharmacodynamic effects [7]. However, the use of H1 blockers is neither prohibited nor recommended in the current acute coronary syndrome guidelines. After achieving hemodynamic stability, we recommend using H1 antagonists in patients with Kounis syndrome.

2.2.2. H-2 blockers

The benefit of administering H2 antagonists once the anaphylaxis has occurred is unclear. The guidelines recommend considering ranitidine at 50 mg in adults and 1 mg/kg in children injected parenterally over 5 min [6]. However, Lin et al. reported the combination of an H2 antagonist with an H1 antagonist had better results than H1 treatment alone in acute allergic syndromes [8]. This issue is also discussed in the practice guidelines, and the combination of diphenhydramine with ranitidine is recommended over diphenhydramine alone therapy. However, these agents have a much slower onset of action than epinephrine and should never be used alone in the treatment of anaphylaxis [6]. Current guidelines state that these agents are second-line therapy after epinephrine. Histamine may have effects unrelated to allergic disease; it induces tissue factor expression which mediates thrombus formation in inflammation and vasospasm [9]. This function of histamine is potentially important and suggests a new target in the treatment of acute coronary syndromes, vasospastic angina, and Kounis syndrome. In addition, H2 blockers may prevent gastrointestinal bleeding in patients with acute coronary syndromes who will receive anti-platelet and antithrombotic drugs. We suggest using both H1 and H2 antihistaminic drugs in patients with Kounis syndrome.

2.2.3. Corticosteroids

Corticosteroids are potent anti-inflammatory and immunosuppressive agents and have a major role in the treatment of allergic reactions. Steroids have no immediate benefit for the first four to 6 h even when administered parenterally in managing anaphylaxis but may prevent recurrent or protracted anaphylaxis. Guidelines recommend considering systemic glucocorticosteroids (intravenously every 6 h at a dosage of 1 to 2 mg/kg/day) for patients who experience severe or prolonged anaphylaxis. Oral corticosteroids (prednisone 0.5 mg/kg) are recommended for less critical anaphylactic episodes.

Corticosteroids impair wound healing and scar formation which could cause myocardial wall thinning, cardiac aneurysms and cardiac wall rupture [10]. A meta-analysis of the studies of corticosteroid treatment in acute myocardial infarction reported no harm and possible mortality benefit with these drugs in acute myocardial infarction [11]. Corticosteroids have also been used successfully in the treatment of refractory vasospastic angina, particularly when the patients have an allergic diathesis [12]. Therefore, the use of corticosteroids in the

treatment of Kounis syndrome needs more investigation but is probably safe and appropriate.

2.2.4. Epinephrine

Whether or not to use epinephrine is a challenging decision in acute coronary syndromes secondary to an allergic reaction. Epinephrine is a life-saving medication in anaphylaxis; however, it has a narrow therapeutic window. In concurrent cases of allergic reaction and acute coronary syndrome, its risks may outweigh the benefits. First, it can aggravate the ischemia, prolong QTc interval, and induce coronary vasospasm and arrhythmias. Elderly patients, especially with a history of hypertension and coronary artery disease, are prone to these side effects. Therefore, epinephrine should be used even more cautiously in this group. Second, the use of intravenous epinephrine is still controversial in severe allergic reactions. It should be considered in patients with severe hypotension or cardiac arrest who do not respond to aggressive fluid resuscitation. The intravenous route of epinephrine administration can cause uncontrolled elevation in blood pressure and precipitate intracranial bleeding. Intramuscular use of epinephrine is the safer and preferred route of administration unless the patient has severe anaphylaxis. Third, most epinephrine preparations contain sulfite as a preservative and an antioxidant which itself may trigger anaphylaxis in sensitive individuals. Finally, some patients may have received beta-blockers in the initial management of the acute coronary syndrome, and the usual dose of epinephrine may be ineffective. It may also promote more vasospasm secondary to unopposed alpha adrenergic effect in patients who have received beta-blocking agents. Glucagon infusion (1 to 5 mg, intravenously over 5 min, followed by infusion 5 to 15 µg/min) can be used for patients who are already on beta-blockers or received them during the management of the acute coronary syndrome. Methoxamine, a potent alpha agonist, can also be considered in patients who do not respond to epinephrine.

Consensus opinion on epinephrine use during anaphylaxis favors epinephrine administration as soon as anaphylactic symptoms occur (strength of recommendation: A) [6,13]. According to the current guidelines, there is no absolute contraindication to epinephrine use in anaphylaxis. The recommended dose and route is 0.2–0.5 mg of aqueous epinephrine (1:1000) administered intramuscularly in the thigh every 5–15 min. In patients with cardiac arrest intravenous epinephrine (1:10,000 to 1:100,000) can be considered. Obviously, these recommendations arise from experiences with all types of anaphylaxis in which most patients did not have a concurrent acute coronary syndrome. More case studies are needed to establish the appropriate use of epinephrine in patients with Kounis syndrome.

2.2.5. Intravascular volume replacement

Up to 40% of intravascular volume moves into the interstitial space causing hypovolemia and hemoconcentration. Volume expansion is an important and essential treatment of anaphylaxis (strength of recommendation: B). In an adult, normal saline, lactated Ringer's solution, or colloid solutions should be administered at a dose of 25–50 ml/kg initially.

Patients with Kounis syndrome may develop left ventricular dysfunction during the insult. Left ventricular end-diastolic pressure may rapidly rise, and extreme amounts of fluid replacement could cause pulmonary edema and respiratory failure. Patients with Kounis syndrome may require additional hemodynamic monitoring and early assessment of left ventricular systolic functions with echocardiography.

2.2.6. Mast cell stabilizers

Mast cell activation is the primary mechanisms resulting in Kounis syndrome. These agents may have the potential to relieve allergic reactions and decrease thrombotic events. Although their efficacy and potency is questionable, mast cell membrane stabilizers (e.g., sodium cromoglycate, and ketotifen) may be considered in patients

who develop acute coronary syndromes after drug reactions and have been used in some cases.

2.2.7. Kounis literature

Currently, the treatment guidelines for the patients with Kounis syndrome have not been established, and most of the information about the treatment of this syndrome comes from individual case reports or case series. Recently, Ridella et al. reviewed the literature on Kounis syndrome cases following beta-lactam antibiotic administration [14]. This review demonstrated that most cases have been treated with steroids (76%), H1 blockers (70%), nitroglycerin (47%), and H2 blockers (35%). Epinephrine was used only in 23% of the cases. Aspirin was used in 18% of the cases. In general, the overall response rate was excellent, and no mortality was reported. The number of cases is too limited to reach definitive conclusions about the treatment of Kounis syndrome, but most clinicians appear to avoid the use of both aspirin and epinephrine.

3. Recommendations

Acute coronary syndromes secondary to allergic reactions are associated with significant morbidity and mortality in hypersensitive individuals. The systemic allergic response caused by inflammatory mediators should be controlled early in the management of these patients.

1. All patients should be questioned carefully regarding their allergy profile before their treatment with a potentially allergic drug such as a beta-lactam antibiotic.
2. Kounis syndrome should be considered in young, healthy patients with no atherosclerotic risk factors when they develop acute coronary syndrome (especially inferior myocardial infarction) after administration of potentially allergic agent. These patients need treatment with steroids, antihistamines, fluid resuscitation, possibly epinephrine, oxygen, and antithrombotics before transfer to the cardiac catheterization laboratory.
3. The treatment should both dilate coronary vessels and suppress the allergic reaction. Vasodilator drugs, including nitrates and calcium channel blockers, should be considered first-line therapy in young and previously healthy individuals since vasospasm is the primary mechanism. Acute coronary syndrome protocol should be followed in patients with a type II variant.
4. These patients should follow-up in cardiology and allergy clinics following the hospital discharge. A full cardiologic work-up, including a 12-lead ECG, echocardiogram and cardiac risk factor modification, is necessary.

An allergy work-up should include the assessment of other allergies to food, insect stings and other environmental agents. Skin tests and food challenges may be useful in identifying the culprit agent.

- a) Food allergy: A reliable history is critical. Food allergy testing (prick test) has a 50% false positive reaction. Sensitivity is very high at about 95%. In the presence of convincing a history, a positive skin prick test for suspected food essentially confirms the etiologic diagnosis of anaphylaxis. A negative skin test with a particular food rules out that food as a cause of anaphylaxis. If skin test is negative or equivocal, allergen-specific IgE can be detected with radioallergen sorbent testing (RAST). In general skin tests are more sensitive than blood tests. Ultimate confirmation may require a single-blind or double-blind food challenge by an experienced clinician; this approach remains the gold standard for the diagnosis of food allergy.
- b) Drug allergy: Many drugs, biological agents, hormones, and dyes can produce IgE mediated systemic symptoms resulting in anaphylaxis. The most common drugs are penicillin, sulfa, NSAID, and tetracy-

cline. Again, history is critical for implicating a drug as the causal factor for anaphylaxis. For most of the drugs, except for penicillin, there is no standardized skin test or blood test (RAST) available. Specific IgE against major and/or minor determinants of penicillin metabolites can occur. Blood tests (RAST testing) can detect IgE antibody directed only to major determinants. However, the most serious anaphylactic reaction with penicillin is secondary to IgE directed against the minor determinants which cannot be detected by RAST testing. In most cases the diagnosis is clinical.

- c) Stinging insect hypersensitivity: If the clinical history is relevant, the diagnosis should be confirmed by skin test. If the skin test is negative but the clinical history supports this diagnosis, RAST testing for stinging insect hypersensitivity is available. In case of stinging insect induced anaphylaxis, the diagnosis should be confirmed since desensitization is absolutely indicated and is highly successful (about 98%).

4. Summary

Kounis syndrome is a complex acute coronary syndrome which requires rapid treatment decisions. Most of the information on this syndrome comes from case reports or small case series. Controlled trials will never be done given the complexity of the presentation. We recommend the establishment of an international registry to collect standardized information on these patients.

Conflict of interest

None.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [15].

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