Original Article

The more allergens an atopic patient is exposed to, the easier and quicker anaphylactic shock and Kounis syndrome appear: Clinical and therapeutic paradoxes

N. G. Kounis, A. Mazarakis[1], G. Almpanis[1], K. Gkouias[1], G. N. Kounis, G. Tsigkas[2]

[1]Departments of Medical Sciences, Patras Highest Institute of Education and Technology,[1]Cardiology, " Saint Andrews" State General Hospital, [2]Cardiology, University of Patras Medical School, Patras, Achaia, Greece

Address for correspondence:
Prof. Nicholas G Kounis, 7 Aratou Street, Queen Olgas Square, Patras - 26221, Achaia, Greece.
E-mail: ngkounis@otenet.gr

Abstract

Kounis syndrome is a condition that combines allergic, hypersensitivity, anaphylactic or anaphylactoid reactions with acute coronary syndromes including vasospastic angina, acute myocardial infarction and stent thrombosis. This syndrome is a ubiquitous disease affecting patients of any age, involving numerous and continuously increasing causes, with broadening clinical manifestations and covering a wide spectrum of mast cell activation disorders. Drugs, environmental exposures and various conditions are the main offenders. Clinical and therapeutic paradoxes concerning Kounis syndrome therapy, pathophysiology, clinical course and causality have been encountered during its clinical course. Drugs that counteract allergy, such as H2-antihistamines, can induce allergy and Kounis syndrome. The more drugs an atopic patient is exposed to, the easier and quicker anaphylaxis and Kounis syndrome can occur. Every anesthetized patient is under the risk of multiple drugs and substances that can induce anaphylactic reaction and Kounis syndrome. The heart and the coronary arteries seem to be the primary target in severe anaphylaxis manifesting as Kounis syndrome. Commercially available adrenaline saves lives in anaphylaxis but it contains as preservative sodium metabisulfite and should be avoided in the sulfite allergic patients. Thus, careful patient past history and consideration for drug side effects and allergy should be taken into account before use. The decision to prescribe a drug where there is a history of previous adverse reactions requires careful assessment of the risks and potential benefits.

Key words: Anaphylaxis, cesarean section, clinical paradoxes, Kounis syndrome, ranitidine

RANITIDINE FOR ALLERGY THAT INDUCES ALLERGY!

Ranitidine, cimetidine, and famotidine are H2-antihistamines which are used quite often for the treatment of anaphylactic reactions. In the National study of US emergency department visits[1] for acute allergic reactions, H2-antihistamine prescriptions increased from 7% to 18% of visits from 1993 to 2004.[1] H2-antihistamines, like H1-antihistamines, are inverse agonists, not competitive antagonists or blockers as originally thought. They have a preferential affinity for the inactive state of H2-receptors, stabilize the receptors in this conformation, and consequently shift the equilibrium toward the inactive state.[2] These substances are used only in combination with H1-antihistamines. When they administered concurrently, they decrease urticaria, flushing, headache, hypotension, and rhinorrhea.[3] In patients with chronic urticaria, antihistamines suppress wheal and flare by 10-15%, but they do not relieve itching.[3] In patients with mild acute allergic reactions, they enhance relief of urticaria and tachycardia but have no significant effect on

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itching or other symptoms. Despite the above beneficial effects on anaphylactic symptomatology, cimetidine,[4] famotidine,[5] and ranitidine[6] can themselves induce severe anaphylactic reactions and shock.[5,6] In the very important report published in this Journal,[6] a 25-year-old primigravida with no past history of allergy was posted for the emergency cesarean section for oligohydramnios. She was given, correctly, for anesthesia, lactated ringer solution, hyperbaric bupivacaine, oxytocin, midazolam, pethidine, methylergometrine and after 5 min 50 mg ranitidine hydrochloride intravenously. However, she immediately developed an allergic reaction and she started complaining of itching, became restless, became flushed, and was coughing. Despite administration of H1-antihistamine pheniramine maleate, hydrocortisone and deriphyllin (etofylline and theophylline) she developed anaphylactic shock. The patient was finally recovered with repeated doses of adrenaline.

THE MORE DRUGS, THE EASIER ANAPHYLAXIS

The initiation of allergic inflammation takes place when allergens cross-bridge their corresponding, receptor-bound, immunoglobulin (Ig) E antibodies on the mast cell or basophil cell surface. These cells degranulate and release their mediators when the critical number of bridged IgE antibodies reaches the order of 2000 out of maximal number of some 500 000-1000 000 IgE antibodies on the cell surface.[7] A total of approximately 1000 bridges are necessary to induced mast cell degranulation. However, recent findings indicate that mast cells can be activated by nonallergic triggers often without degranulation, but with selective release of potent and vasoactive compounds.[8] Clinical studies indicate that allergic patients simultaneously exposed to several allergens have more symptoms than monosensitized individuals.[9] On the contrary, IgE antibodies with different specificities can have additive effects and small, even subthreshold numbers of them can join forces and trigger the cells to release their mediators. This can happen when the patient is simultaneously exposed to the corresponding antigens.[10] This data suggest that a possible sensitization should not be clinically evaluated as a consequence of exposure to a single drug but rather viewed in the context of potential sensitization to multiple drugs. The described patient had received a total 10 different drugs in an effort to induce anesthesia and to treat the allergic reaction to ranitidine. All these substances have been incriminated as inducing mild or severe allergic reactions, namely bupivacaine, hydrocortisone, methylergometrine, midazolam, oxytocin, pethidine, pheniramine, ranitidine, lactated ringer, and theophylline.[11-20]

ANAPHYLAXIS IN ANESTHESIA

Every anesthetized patient is under the risk of multiple drugs and substances that can induce anaphylactic reaction and Kounis syndrome.[21] Antibiotics, apronitin, blood transfusion, chlorhexidine, contrast media, colloids, dyes, H_1-and H_2-antihistamines, hypnotic agents, latex exposure, local anesthetics, neuromuscular blocking drugs, opioids, protamine, and several other specific agents depending on the kind and area of intervention are some of the offenders. While anaphylaxis can occur shortly after induction of anesthesia, it may take place at any time with all potentially allergenic substances.[22] The clinical features are involving mainly the cardiovascular system and especially the coronary arteries manifesting as Kounis syndrome.[23] Bronchospasm, cutaneous, or mucus involvement are also presenting features. Anaphylactic symptoms and signs are grated[24] as Grade I involving cutaneous-mucus signs, Grade II involving mild cutaneous-mucus signs that may be combined with cardiorespiratory signs, Grade III involving cutaneous-mucus signs and/or bronchospasm with cardiovascular collapse, and Grade IV denoting cardiac arrest.[24] The latter two grades correspond with the Kounis syndrome symptomatology. Diagnosis of anaphylaxis during anesthesia can be achieved by measuring of histamine which has very short (8-10 min) plasma half-life, tryptase which has intermediate half-plasma time (90 min), specific IgEs for thiopental, propofol, antibiotics, suxamethnium, quaternary (choline analog), ammonium (is thought to be the allergenic determinant in neuromuscular blocking drugs) and for other given agents. Additionally, prick tests followed by intradermal tests can corroborate the diagnosis and identify the culprit cause of anaphylaxis and/or of Kounis syndrome during anesthesia. Ranitidine is widely used during anesthesia especially in obstetric cases for aspiration prophylaxis. Therefore, most cases of ranitidine-induced anaphylaxis are encountered during anesthesia. In the described case 50 mg of ranitidine was given intravenously 5 min following lactated ringer solution, hyperbaric bupivacaine, oxytocin, midazolam, and pethidine. Did all these substances join forces and directly or via IgE-induced mast cells degranulation?

KOUNIS SYNDROME: THE HYPERSENSITIVITY ASSOCIATED ACUTE CORONARY SYNDROME

This syndrome was described 20 years ago as allergic angina and allergic myocardial syndrome, and is defined today as the concurrence of acute coronary syndromes with conditions associated with mast cell degranulation, involving interrelated and interacting inflammatory cells, and including allergic or hypersensitivity and anaphylactic

or anaphylactoid insults. It is caused by inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, platelet activating factor, and a variety of cytokines and chemokines released during the activation process. A subset of platelets bearing FCγRI, FCγRII, FCεRI, and FCεRII receptors are also involving in the activation cascade.[25] Today Kounis syndrome is ubiquitous disease affecting patients of any age, involving numerous and continuously increasing causes, with broadening clinical manifestations and covering a wide spectrum of mast cell activation disorders. Indeed, Kounis-like syndromes have been described that affect the cerebral and mesenteric arteries and constitutes a manifestation of mast cell activation syndromes.[26] The most recent offenders are the scombroid syndrome which is called also histamine fish poisoning, the Anisakis simplex which is a common parasite of fish which is able to sensitize humans via the alimentary tract, the Gelofusine substance, latex exposure, the drug losartan and Fish flesh contains the amino acid histidine and when fish is infected by gram negative bacteria that contain the enzyme histidine decarboxylase, then this enzyme converts histidine to histamine which induces Kounis syndrome. The gelofusin substance is a bovine gelatin administered to maintain intravascular volume. Gelofusin is component of various vaccines for children and constitutes the main cause of sensitization to children. It should be always remembered that exposure to such substances can occur through the "kiss of death" and the "dog licking."[27,28] "The kiss of death" occurs when a person after consumption of shellfish or peanuts kisses passionately his or her friend who happens to be allergic to these substances. Furthermore a dog, who receives antibiotic such as penicillin for any infection, can be very dangerous when he licks his penicillin allergic master. Three variants of Kounis syndrome have been described: [29] Type I variant which includes patients with normal or nearly normal coronary arteries without predisposing factors for coronary artery disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm without increase of cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins. Type II variant which includes patients with culprit but quiescent preexisting atheromatous disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or coronary artery spasm together with plaque erosion or rupture manifesting as acute myocardial infarction. Type III variant which includes patients with coronary artery stent thrombosis in whom aspirated thrombus specimens stained with hematoxylin-eosin and Giemsa demonstrate the presence of eosinophils and mast cells, respectively. The described patient developed anaphylactic shock with feeble peripheral pulses, tachycardia, and cardiovascular collapse. Echocardiography showed empty cardiac chambers. Although electrocardiogram was not given and troponins and cardiac enzymes were not described, a type I variant of Kounis syndrome cannot be excluded.

A PATHOPHYSIOLOGIC PARADOX: ISCHEMIC MYOCARDIAL DAMAGE IS PRIMARY EVENT DURING ANAPHYLACTIC SHOCK

So far, it is generally believed that anaphylactic shock is the result of systemic vasodilation, reduced venous return, leakage of plasma, and volume loss due to increased vascular permeability ensuing to depression of cardiac output that contributes to coronary hypoperfusion with subsequent myocardial damage. However, experimental and clinical studies indicate that the human heart can be the primary site and the target of anaphylaxis resulting in the development of Kounis syndrome. In experimental anaphylaxis[30] with ovalvumin sensitized guinea pigs, it was shown that soon after antigen administration the left ventricular end, diastolic pressure rose significantly indicating pump failure and the arterial blood pressure rose also significantly, while the cardiac output decreased by 90%, The blood pressure started declining steadily after 4 min. It was concluded that the rapid increase in left ventricular end diastolic pressure suggests that decreased venous return and volume loss due to an increase of vascular permeability are unlikely to be the primary causes of the documented depression of cardiac output and the view that the registered anaphylactic damage might be due to peripheral vasodilation can be definitely excluded. In the clinical setting,[31] there are current reports according to which patients with anaphylactic cardiac shock do not respond to fluid replacement but recover with current acute myocardial infarction protocol and antiallergic treatment thus denoting that the heart is primarily affected. Furthermore, other recent experiments[32] have shown that anaphylactic shock decreases cerebral blood flow more than what would be expected from severe arterial hypotension. This was attributed to the early and direct action of anaphylactic mediators on cerebral vessels. Indeed, mast cell mediators such as histamine, chymase, and leukotrienes released locally and in the systemic circulation can induce cerebral artery spasm and platelet-activating factor can reduce cerebral blood flow leading to postischemic hypoperfusion. Therefore, cerebral ischemia and brain injury following anaphylactic shock could be due to direct action of anaphylactic mediators on the cerebral arterial system and not solely due to arterial hypotension. The same seems to apply for the coronary vessels and the cardiac myocardium.

THE ADRENALINE PARADOX

Apart from their adrenergic action, commercially available preparations of adrenaline usually contain as a preservative, sodium metabisulfite. Sodium metabisulfite is commonly used as an antioxidant in the food and pharmaceutical industries. There are reports of hypersensitivity, anaphylaxis, and even death from Kounis syndrome from sulfite administration. Anaphylactoid shock has been reported during epidural anesthesia for cesarean section, in which the responsible agent was metabisulfite, as additive agent of adrenaline-containing local anesthetic.[33] This situation poses a therapeutic dilemma in the sulfite-sensitized patients who suffer from anaphylactic shock. Only few physicians are aware of this treacherous association. Although adrenaline is still the primary drug for anaphylaxis, avoidance of medications that contain metabisulfites as preservatives, including adrenaline, is suggested for patients with definite sensitization to sulfites. In this situation, a possible alternative is glucagon which has been used successfully for treatment of anaphylaxis in patients taking β-blockers.[34] Today, sulfite-free adrenaline is available (American Regent Inc, USA) for patients sensitive to sulfites. Fortunately, the described patient received repeated doses of adrenaline and had an excellent and quick recovery with uneventful course.

CONCLUSION

Mother Nature has given to us, on several occasions, natural paradigms of how to treat but also several paradoxes of how not to treat. Every physician should bring in mind that commonly used, generally safe drugs, may occasionally cause serious anaphylactic effects. Such drugs may also join forces in order to do their adverse effect. Thus, careful patient history and consideration for drug side effects and allergy should be taken into account before use. The decision to prescribe a drug where there is a history of previous adverse reactions requires careful assessment of the risks and potential benefits. We all as physicians should always have in mind the Aristotle's (384-322 B.C.) dictum:

"Not many is the good, but in the good, the many" (Ouk en tō Pollo to eu, but en to eu to poly=ΟΥΚ ΕΝ ΤΩ ΠΟΛΛΩ ΤΟ ΕΥ ΑΛΛΑ ΕΝ ΤΩ ΕΥ ΤΟ ΠΟΛΥ).

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