

Brain injury due to anaphylactic shock: broadening manifestations of Kounis syndrome

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Abstract

Soufras GD, Kounis GN, Kounis NG. Brain injury due to anaphylactic shock: broadening manifestations of Kounis syndrome. *International Endodontic Journal*.

Anaphylactic shock is a real and life threatening medical emergency which is encountered in every field of medicine. The coronary arteries seem to be the primary target of anaphylaxis resulting in the development of Kounis syndrome. Kounis syndrome is a pan-arterial anaphylaxis-associated syndrome 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. Recently, Kounis-like syndrome affecting the cerebral arteries was found to be associated with mast cell activation disorders. In anaphylactic shock, the decrease of cerebral blood flow is more than what would be expected from severe arterial hypotension. This is attributed to the early and

direct action of anaphylactic mediators on cerebral vessels. While adrenaline is a life saving agent in the treatment of anaphylactic shock, it contains sodium metabisulfite as preservative and should be avoided in sulfite allergic patients. Potential allergens encountered in endodontic practice include formocresol, zinc compounds thiurams, sodium dimethyldithiocarbamate, and mercaptobenzothiazole that might have synergistic action. All these agents together with analgesics, antibiotics, antiseptics, formaldehyde, latex, local anaesthetics and metals used in dental practice, in general, can induce anaphylactic shock. Practitioners should be aware of these consequences. A careful history of previous atopy and reactions is of paramount importance for safe and effective management.

Keywords: adrenaline, anaphylaxis, brain injury, Kounis syndrome.

Received 2 April 2013; accepted 13 June 2013

Introduction

In the report by Ding *et al.* (2013) published in this Journal, a 45-year-old female with a history of allergy to ceftriaxone developed anaphylactic shock 10 min after application of a formocresol (formaldehyde cresol and phenolic protein-coagulating compound)-soaked cotton pellet in the pulp chamber with zinc phosphate cement. She developed signs of hypersensitivity including dizziness, shortness of breath,

nausea and lost consciousness whilst her systolic blood pressure dropped to 60 mmHg. She was treated with adrenaline, corticosteroids and intravenous infusion of 5% dextrose. The patient regained consciousness after 23 min. However, after regaining consciousness, she began complaining of a headache, which increased in severity over time. Her blood pressure returned to normal 4 h after she lost consciousness. Magnetic resonance imaging revealed hyperintensity on T2-weighted imaging and hypointensity on T1-weighted imaging, corresponding to swelling of the gyrus in the cerebral watershed territory of the left parietal-occipital lobe. The patient was diagnosed with brain injury due to anaphylactic shock caused by formocresol. Traditionally, formocresol and related

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agents are used as disinfectants for root canal treatment, pulpotomy and root canal sealants. Anaphylactic shock is a real and life-threatening medical emergency, and its consequences are attributed to the mediator action on tissue vasculature.

Kounis syndrome: a pan-arterial hypersensitivity-associated disorder

Kounis syndrome (Kounis 2006, Biteker 2010a) is a combination of acute myocardial injury, from coronary artery spasm and/or myocardial infarction with conditions associated with mast cell activation, involving interrelated and interacting inflammatory cells and includes anaphylactic or anaphylactoid, and allergic or hypersensitivity insults. It is caused by preformed and newly synthesized inflammatory mediators released during the anaphylactic process. Platelets bearing in their surface FC γ RI, FC γ RII, FC ϵ RI and FC ϵ RII receptors are also involved in the activation cascade. Recently, a Kounis-like syndrome has been described that affects not only the coronary arterial system, but the cerebral (González-de-Olano *et al.* 2011) and mesenteric arteries (Goto *et al.* 2012). It is anticipated that the entire arterial system is vulnerable to allergic, hypersensitivity, anaphylactic or anaphylactoid events. Three variants of Kounis syndrome have been described (Biteker 2010b, Kounis *et al.* 2011). Coronary spasm or type I variant, which applies to patients with normal or nearly normal coronary arteries, in whom anaphylactic reaction can progress to myocardial infarction. Coronary thrombosis or type II variant, which applies to patients with culprit, but quiescent, pre-existing atheromatous disease in whom anaphylactic reaction can result in acute myocardial infarction. Coronary stent thrombosis or type III variant, which applies to patients with hypersensitivity to any implanted intracoronary stent component that can result in devastating intrastent thrombotic occlusion. Today, Kounis 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.

The brain in anaphylaxis

In the report by Ding *et al.* (2013), the patient presented swelling of the gyrus in the cerebral watershed territory of the left parietal–occipital lobe, and was

diagnosed with brain injury due to anaphylactic shock caused by formocresol.

Historically, formocresol and related agents are used as disinfectants for root canal treatment, pulpotomy and root canal sealants. It is known that formaldehyde (paraformaldehyde and trioxymethylene), a primary component of formocresol, can act as antigen (Leventhal *et al.* 2012) that can provoke anaphylactic reactions. In an effort to treat anaphylaxis and to counteract hypotension, the authors correctly administered corticosteroids, oxygen and adrenaline.

Mast cells and other interrelated and interacting inflammatory cells such as macrophages and T-lymphocytes are well known for their participation in allergic and anaphylactic reactions. Although mast cells are numerically a minority in this inflammatory cascade, they influence decisively the anaphylactic process. During anaphylaxis, mast cell surface bound immunoglobulin E (IgE) complexes with specific antigen cause mast cell degranulation resembling a foil package of popcorn popping until their contents overflow. Mast cells are ubiquitous in the human body including the brain, which does not suffer from allergic reactions because IgE does not cross the blood–brain barrier. Despite this ubiquity, mast cell degranulation occurs only in about 10% or so atopic individuals (Theoharides 2002). Mast cell pre-forms and stores in almost 500 secretory granules and makes *de novo*, during anaphylactic stimulation, many inflammatory molecules which contain a host of vasoactive mediators such as histamine, tumour necrosis factor- α , heparin and neutral proteases such as tryptase, chymase and cathepsin-D. These cells are resident within the cerebral vasculature and by releasing their vasoactive mediators promote blood–brain barrier damage, brain oedema, prolonged extravasation and even haemorrhage (Lindsberg *et al.* 2010).

Various symptoms such as tiredness, somnolence or various levels of sleep can be misinterpreted as a normal phenomenon after an allergic reaction. These might well be symptoms of anaphylaxis as a result of reduced brain perfusion induced by airway or circulation problems, which can alter the patient's neurological status (Vetander *et al.* 2011).

Adrenaline in anaphylaxis and its effect on cerebral perfusion

Adrenaline is the drug of choice for anaphylaxis and can be life-saving. Therefore, adrenaline is wisely

given together with corticosteroids in cases of anaphylactic shock. In the paper of Ding *et al.* (2013), the atopic patient was allergic to ceftriaxone and developed anaphylactic shock soon after application of soaked cotton pellet with zinc phosphate cement in the tooth pulp chamber. There are some instances where these substances can act as antigens, and worsen anaphylactic reaction. For example, a therapeutic dilemma arises in the sulphite allergic patient. Every commercially available preparation of adrenaline contains sodium metabisulphite as a preservative, according to Drug Facts and Comparisons (a standard pharmacy reference published by Wolters Kluwer and updated monthly). Sodium metabisulphite is commonly used as an antioxidant in food and pharmaceutical industries. Anaphylactic shock has been reported during epidural anaesthesia for Caesarian section in which the responsible agent was metabisulphite an additive agent of adrenaline containing local anaesthetic (Soulat *et al.* 1991). Unfortunately, few physicians are aware of this association. Fortunately, nowadays, sulphite-free adrenaline is commercially available for use in sulphite sensitive patients (American Regent Inc, Shirley, NY, USA). On the other hand, the involvement of all these drugs can act synergistically and cause IgE-mediated mast cell degranulation. Anaphylaxis is initiated by allergens cross-bridging their corresponding receptor bound immunoglobulin IgE or IgG antibodies on mast cell surface. A total of 1000 bridges are necessary to degranulate mast cell out of a maximum number of some 500 000–1 000 000 IgE molecules. It might be possible to accumulate the critical number of bridges by more than one non-cross-reactive antigen and its corresponding IgE (Mazarakis *et al.* 2012), which means that these bridges can be made by antigens of different specificities as in the described case. It looks likely that the more antigens an atopic patient with anaphylaxis is exposed to, the easier and quicker mast cell degranulation occurs. The use of intravenous (IV) adrenaline is still controversial in anaphylactic reactions. It should be considered in patients with severe hypotension or cardiac arrest who do not respond to aggressive fluid resuscitation. IV use can cause uncontrolled elevation in blood pressure and precipitate intracranial bleeding. Intramuscular use of adrenaline is safer and the preferred route of administration unless the patient has severe anaphylaxis. In patients on beta-blockers, the usual dose of adrenaline may be ineffective. It may also promote more vaso-spasm secondary to unopposed alpha-adrenergic

action. Glucagon may be considered for patients who are already receiving beta-blockers. The recommended dose and route is 2–5 mg of aqueous adrenaline (1 : 1000) administered intramuscularly in the thigh every 5–15 min. In patients with cardiac arrest, IV adrenaline (1 : 10 000–1 : 100 000) can be considered (Kounis *et al.* 2011). The action of adrenaline on cerebral oxygenation and cerebral microcirculation seems to be controversial. It has been demonstrated, recently, that clinical doses of adrenaline infusion result in a delayed increase in cortical blood volume due to an increase in oxyhaemoglobin, which is consistent with vasodilation (Steinback *et al.* 2012). On the other hand, carotid arterial injection of adrenaline has induced cerebral infarction in a 24-year-old female patient suffering from septic shock (Saxena & Sharma 2005). In a domestic pig model, adrenaline through its 1-agonist action had adverse effects on cerebral microvascular blood flow such as to increase the severity of cerebral ischaemia during cardiopulmonary resuscitation (Ristagno *et al.* 2009). Horisawa *et al.* (2001) developed an ADP/adrenaline-induced transient cerebral ischaemia model in guinea pigs and thereby evaluated the protective effects of SM-20302. Oral administration of SM-20302 resulted in a significant reduction in ischaemic area, and improvement in neurological deficits as well as the recovery of lactate content. The authors suggested that these results indicate that SM-20302 may be useful in the prevention of transient ischaemic attacks and stroke.

Anaphylactic shock decreases cerebral blood flow more than would be expected from severe arterial hypotension

It is generally believed that during anaphylactic shock systemic vasodilation, reduced venous return, leakage of plasma and volume loss due to increased vascular permeability.

The ensuing depression of cardiac output contributes to cerebral and myocardial hypoperfusion with subsequent cerebral and myocardial damage. Indeed, during anaphylactic shock, circulating blood volume may decrease by as much as 35% within 10 min due to transfer of intravascular fluid to extravascular space and severe vasodilation resistant to adrenaline and responding only to other potent vasoconstrictors has been reported (Schummer *et al.* 2004). In a recent study (Davidson *et al.* 2012), it was found that anaphylactic shock decreases cerebral blood flow

more than what would be expected from severe arterial hypotension. The authors of this paper concluded that, in anaphylactic shock, severe impairment of the cerebral blood flow takes place, which could not be explained by the level of arterial hypotension. In their experiments, using a rat model of anaphylaxis, the tissue oxygen partial pressure decreased very rapidly, as early as 1 min following the onset of anaphylaxis, and this was attributed to the early and direct action of anaphylactic mediators on cerebral vessels. Indeed, mast cell mediators such as histamine, chymase, leukotrienes can induce cerebral artery spasm, and platelet-activating factor can reduce cerebral blood flow leading to post-ischaemic hypoperfusion. Therefore, cerebral ischaemia 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.

There is experimental and clinical evidence that the primary target of the released anaphylactic mediators is the arterial vasculature resulting in damage of the corresponding brain or myocardial tissue. In an experiment with ovalbumin sensitized guinea pigs, it was concluded that the registered anaphylactic damage is not due to arterial hypotension and this can be definitely excluded (Felix *et al.* 1990). There are, currently, patients with anaphylactic cardiac shock who did not respond to intravenous fluid administration and anti-allergic therapy, but required a coronary event treatment protocol (Gangadharan *et al.* 2013).

Allergic reactions are common whilst severe anaphylaxis and shock are less common in everyday practice

Mild allergic reactions occur quite often in every day practice, but severe anaphylaxis and anaphylactic shock occur less commonly. However, an initially mild reaction could progress to a severe and fatal reaction. Lifetime personal risk of anaphylaxis is pre-

sumed to be 1–3% with a mortality rate of 1% (Kemp 2007). There are several offenders encountered in everyday dental practice (Table 1). In the paper of Ding *et al.* (2013), the patient was allergic to ceftriaxone, but developed anaphylactic shock after exposure to formocresol (formaldehyde cresol and phenolic protein-coagulating compound). It has been found, recently, that patients with serum baseline tryptase greater than normal have mast cell disorder, either systemic mastocytosis or monoclonal mast cell activation syndrome and are prone to developed immediate and severe anaphylactic reaction (Bonadonna *et al.* 2009). Furthermore, raised salivary levels of mast cell carboxypeptidase may be helpful in confirming that an allergic reaction to drugs has occurred and baseline levels in serum and saliva may be predictive of the severity of future allergic reactions. Therefore, patients with increased serum baseline tryptase might have mutations that lower the stimulus threshold for anaphylaxis and have hyper-responsive mast cell phenotype resulting in the development of severe anaphylaxis and Kounis syndrome (Metcalf & Schwartz 2009).

Conclusion

There is increasing concern with the biocompatibility of dental materials, which can affect biologic activity. Potential allergens include formocresol, zinc compounds, as well as thiurams, sodium dimethyldithiocarbamate and mercaptobenzothiazole that might have synergistic action. Mild, acute, severe including anaphylactic shock and immediate or delayed reactions (Sunay *et al.* 2006) are encountered. Anaphylactic shock is a real and life-threatening medical emergency, and its consequences are attributed to the mediator action on the tissue vasculature. Practitioners should be aware of these consequences. A careful history of previous atopy and reactions is of paramount importance for safe and effective management.

Table 1 Allergic offenders reported to induce anaphylactic shock

Analgesics (salicylates, NSAIDs, codeine)	Latex (gloves, dental dams, syringes, catheters)
Antibiotics (sulphonamides, penicillin, amoxicillin, augmentin, cephalosporins and relative compounds)	Local Anaesthetics (benzocaine, chloroprocaine, novocaine, procaine, tetracaine)
Antiseptics (chlorhexidine)	Metals: nickel, gold, mercury, chromium (crowns, bridges, dentures, inlays, braces, bite plates, spacets)
Foods (nuts, shellfish, milk products, strawberries eaten prior to dental visit)	
Formaldehyde (canal sterilization and disinfection, root canal sealing)	
Formocresol (formaldehyde cresol and phenolic protein-coagulating compound)	

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