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Kounis Syndrome: An analysis of spontaneous reports from international pharmacovigilance database

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ABSTRACT

Introduction: The coincidental occurrence of a cardiac symptomatology (e.g. an acute coronary syndrome or a myocardial infarction), during an anaphylactic or anaphylactoid episode is known as Kounis Syndrome. A variety of drugs, substances, food and environmental exposures are associated with this reaction. There is an exponential increase in the number of published scientific articles reports on this syndrome, but since it is rare, the largest case series published so far included only 10 and 6 patients.
Methods: We searched the global World Health Organization database called VigiBase™ to detect all cases of Kounis Syndrome ever reported (last update December 31st 2014).
Results: We identified 51 cases of Kounis Syndrome reported to International Pharmacovigilance Agency (VigiBase™). All these cases were reported in the period 2010–2014 and almost half cases (22 reports) belonged to the year 2014. Most cases occurred in the USA and non-steroidal anti-inflammatory drugs were the most frequent trigger drugs.
Discussion: We collected pharmacovigilance international data representing the largest case series ever published on the recently identified Kounis Syndrome.

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1. Introduction

The first association of cardiac symptoms and an allergic event date back to 1950 [1,2], while allergic angina and allergic myocardial infarction were first described in 1991 and are known as Kounis Syndrome (KS) [3]. Diagnosis needs the concurrent presence of acute coronary syndrome and an allergic event [3]. This syndrome might result in death by myocardial infarction [4].

During an allergic event, the activation of mast cells leads to histamine, leukotrienes and serotonin release [5]. Depending on the severity of reaction, these mediators cause the involvement of hemodynamic function, with generalized vasodilatation leading to allergic or anaphylactic shock. The same inflammatory mediators can cause a spastic reaction of coronary smooth muscle cells [6] and mast cells [7]. Eosinophils and lymphocytes [8] are found in histological reports.

The clinical manifestations of the syndrome focus on typical cardiac signs and symptoms such as chest pain and electrocardiographic alterations in ST segment or T waves or any degree of hearth block and other arrhythmias; in myocardial infarctions the elevation of cardiac enzymes is also observed. Various allergic or hypersensitivity clinical findings, such as hypotension, pruritus or dyspnoea, complete the typical presentation of the syndrome [3].

There is no standard criteria leading to diagnosis of KS but a cardiac involvement during an allergic reaction is the most typical finding. There is also no agreement on the treatment of KS [9] and therapy is directed to reduction of the inflammatory cascade and allergic reaction through corticosteroids and antihistamines and in managing the acute coronary event. The use of adrenaline is debated since it is the drug of choice in the case of severe allergic reactions [10,11], and it was frequently given to patients with KS reports but it can worsen the cardiac function already compromised by the coronary spasm [9,12] and should be reserved to the most severe cases [13].

The incidence is yet to be determined.

Etiology is unclear. Potentially, any kind of medication can trigger severe allergic reactions and multiple agents were associated with KS. Antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently involved drugs. Moreover, insect bites [14] and drug eluting stents [15,16] have frequently been associated with KS. Notably, during a diagnostic insect sting challenge study, 9.5% of otherwise healthy volunteers developed acute myocardial ischemia [17].

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Despite the rarity of the KS, there is an increasing awareness of physicians on this specific event, in particular when the KS occurred following the use of medicines. The purpose of this study was to collect all the cases of KS based on data available from the most comprehensive pharmacovigilance database and to compare them with the largest case series published in scientific literature.

2. Methods

We searched VigiBase™, the global World Health Organization database for Individual Case Safety Reports (ICSRs) spontaneously collected since 1968, that includes data from over 100 countries (including U.S. and Europe). VigiBase™ is managed by the Uppsala Monitoring Centre on behalf of the World Health Organization. We collected all cases that reported "Kounis Syndrome" as preferred term based on MedDRA dictionary [18] from January 1st 2000 to December 31st 2014.

Data were extracted and analyzed by expert investigators who carefully excluded all reports that were also published in biomedical literature and duplicate case reports.

The following variables were available from the retrieved reports: age, sex, country, year of adverse drug reaction (ADR) occurrence; time to ADR onset (i.e. the delay from drug administration and the occurrence of event); suspected and concomitant drug(s) including and their therapeutic indications; treatment duration; seriousness of the event and clinical outcome.

The narrative was only available for the European cases; thus, an in-depth analysis aimed at identifying underlying risk factors, features of symptomatology, clinical procedures to confirm the diagnosis of KS, and actions taken to manage the event was attempted on the European cases.

A descriptive analysis of the available data estimated the cumulative number of KS cases and their distribution by the selected variables. Data are reported as mean (standard deviation), median (interquartile range), range and number (percentage) as indicated.

3. Results

Through the international pharmacovigilance database VigiBase™ we originally retrieved 67 KS cases worldwide; eliminating 16 duplicate cases or cases already published, a valid sample of 51 cases of KS was identified. All cases were reported from 1st January 2010 to 31st December 2014 and with almost half of the cases pertaining to the last year (Table 1). Patients' characteristics showed a mean age of 46 ± 22 years old (range 2–84) and a prevalence of male subjects of 63%. All but two cases (from Japan) were reported in the United States (n = 32) or European countries (n = 17) (Tables 1 and 2).

Table 1
Characteristics of the 51 cases of Kounis Syndrome.

Age, years, mean (SD)	46 (22)
Female gender (%)	17/49 (35%)
Country	
Japan	2 (3.9%)
USA	32 (63%)
Europe	17 (33.1%)
France	7 (13.7%)
Spain	3 (5.9%)
Italy	2 (3.9%)
Switzerland	2 (3.9%)
Turkey	1 (1.9%)
Netherlands	1 (1.9%)
UK	1 (1.9%)
Year of reporting	
2010	5
2011	11
2012	5
2013	8
2014	22
Time from the suspected drug administration to the Kounis Syndrome	
0–1 day	10 cases
1–3 days	1 case
3–7 days	1 case
>7 days	2 cases
Duration of treatment with the culprit drug	
Up to 1 day	10 cases
2 days	1 case
3 days	1 case
23 days	1 case
90 days	1 case

The time from suspected drug administration to ADR onset, available for 14 out of 51 cases, was equal or less than 1 day in 71% of cases.

Suspected drug classes (Table 3) more frequently reported with KS cases were NSAIDs (in 31 ICSRs), cardiovascular drugs (in 10 ICSRs, including 6 ICSR with adrenaline), antibiotics (8 ICSR) and anesthetics (in 5 ICSRs, including 3 ICSRs with non-depolarizing muscle relaxants). In 32 cases a single suspected drug was reported, while in the remaining 19 cases there were two or more co-administered suspected drugs.

The collected information on the duration of treatment with the suspected drugs showed that the majority of patients started receiving these drugs one day or less before the event, thus highlighting that in our patients KS was an acute event triggered by very short drug exposure.

All cases but one were reported as serious. Three patients died, 28 had favorable outcome and in 20 cases the information on outcome was not available.

An in-depth analysis conducted on 17 European cases (7 from France) with narrative detailed description showed that the most common risk factors consist of cardiovascular disease (6 cases), type II diabetes (3 cases) and drug hypersensitivity (3 cases). The most frequent clinical investigations to confirm KS were laboratory examinations (10 cases including 6 cardiac biomarkers) and electrocardiograms (7 cases). The actions frequently taken to manage KS were drug withdrawn and the treatment of the allergic episodes with corticosteroids, adrenaline and antihistaminic drugs (Table 4). Only two reports mentioned performing coronarography following Kounis Syndrome.

4. Discussion

4.1. Key findings

Using worldwide recent pharmacovigilance reports we were able to identify the largest case series on KS. This is probably an underdiagnosed syndrome and physicians have only recently been aware of its existence. Even if KS was first described in 1991 by Kounis NG, the first pharmacovigilance report belonged to 2009, based on Turkish case series, and in 2010 in our analysis. Twenty-two of the 51 reported cases were identified in 2014, demonstrating increasing awareness by health care professional on this syndrome. Our data confirm that the most common implicated drugs are NSAIDs and antibiotics as previously reported [19,20]; however, in our analysis also cardiovascular drugs appear to be often involved. Interestingly only one out of 17 narrative reports mentioned performing coronarography while this test

Table 2
Details of the European (17 cases) and US (32 cases) patients.

	European (17 cases)	USA (32 cases)
Age, mean	58	42
Female	4	12
Suspected drug		
Non-steroidal anti-inflammatory drugs	5	17
Antibiotics	4	1
Cardiovascular	2	7[a]
Anesthetics	1	4
Seriousness		
Caused or prolonged hospitalization	5	22
Life threatening	10	5
Fatal	2	1
Unknown		4
Outcome		
Fatal	2	1
Recovered/resolved	14	15
Unknown	1	17

[a] 6 cases with adrenaline; 1 case with both thrombin inhibitor and GPIII/II inhibitor as suspected drug in the same patient.

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