



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 heart 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 drug 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

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

63%. All but two cases (from Japan) were reported in the United States ($n = 32$) or European countries ($n = 17$) (Tables 1 and 2).

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 withdrawal 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.

Table 3

Suspected drugs for Kounis Syndrome in 51 patients reported to international pharmacovigilance (in this table more than one suspected drug is reported for some patients).

Suspected drug	Number
NSAIDs	31
Acetyl salicylic acid	8
Ibuprofen	9
Naproxen	8
Metamizole	3
Diclofenac	2
Ketoprofene	1
Antibiotics	9
Amoxicillin/clavulanic acid	3
Amoxicillin and piperacillin/tazobactam	4
Levofloxacin, metronidazole	2
Treatment for cardiovascular disease	10
Adrenaline	6
Losartan, clopidogrel, bisoprolol, bivalirudin	1
Contrast medium	2
Sulfurhexafluoride, iobitridol	1
Anesthetics	5
Rocuronium	2
Cisatracurium	1
Isoflurane	2
Other	9
Omeprazol, allopurinol, cisplatin, cyclophosphamide, ondansetron, acetylcysteine, paclitaxel, nickel, sirolimus	1

has always been reported in previous case series [19–22]. This can be attributable to the characteristics of spontaneous reporting with data gathered in a short period and the pieces of collected information are not related to a specific ADR. Our data suggest that such reports are peculiar of an emergency department and that biopsy/arteriography (recommended by current guidelines), requiring a different organization, was probably postponed. When considering the actions taken to manage KS, a situation that requires treatment of both anaphylaxis and acute coronary syndrome [23], in our case series, we noted that more attention was paid to the allergic component of the KS, with cardiac therapies reported only in four cases. In addition, we noted that adrenaline was used in 11 cases to treat allergic reactions and in 6 of these cases adrenaline was a suspected drug for KS.

Table 4

Data of the 17 European patients.

<i>Management for diagnosis (11 cases)</i>	
Electrocardiogram	7
Enzyme levels	
Increase of troponin	5
Increase of triptase	2
Increase of C-reactive protein	2
Increase of brain natriuretic peptide	1
Coronarography	2
Eosinophilia	1
Prick test positive for Amoxicillin	1
Allergologic examination	1
Increase of leukocytes	1
<i>Risk factors (11 cases)</i>	
Cardiovascular disease	6
Drug hypersensitivity	3
Diabetes	3
Shock after the induction of anesthesia	2
Concomitant administration of amoxicillin/clavulanic acid	1
<i>Actions taken (15 cases)</i>	
Drug withdrawn	10
Steroid administration	6
Adrenaline administration	5
Anti-allergic medications	4
Cardiovascular disease treatments	4

4.2. Previous relevant studies

The largest four case series published so far included 10, 6, 5 and 3 patients respectively [19–21,23]. Male patients were more frequent than female and the most frequently described suspected drugs were antibiotics (9 cases) and NSAIDs (4 cases) while there were also non-drug agents (e.g. exercise, insect stings, foods).

The largest case series was a Spanish report on 10 patients with systemic mastocytosis [23]. Half of the cases had drugs as suspected trigger of the syndrome (one case in the setting of general anesthesia) and, for the first time, exercise was suggested to be the culprit of a mast cell activation leading to KS.

A Turkish case series [19] of 6 patients identified antibiotics as the most frequently suspected drug and all patients had elevated serum tryptase levels as indicator of severe mast cell activation. They did not have history of cardiovascular diseases or allergic reactions and, after the clinical manifestation of KS, a coronary angiography was performed in all of them without abnormal or critical signs detected. Conversely, an echocardiographic examination revealed an altered segmental wall motion in all cases, with an increase of troponin I serum levels.

In a Spanish case series [21] of 5 patients elevated serum tryptase levels were measured in all cases and 4 of these had drugs as suspect agents. Allergic diathesis and cardiovascular risk factors were present in two patients together with significant stenosis at coronary angiography. No ecocardiographic examination was performed but in all cases elevation in serum troponin I levels with electrocardiographic alterations confirmed the cardiac involvement.

Three Italian patients with cardiovascular risk factors and treated with antibiotics (indicated as suspected drugs) for dental procedures represent the last case series with at least 3 patients that we identified [20]. Electrocardiographic signs were noted and only in one patient angiographic examination revealed coronary lesions that required percutaneous angioplasty and stenting. In two patients there was an elevation in troponin I, while serum tryptase levels were not measured.

In a recent article by Kounis NG [13], the author reviewed the most important characteristics of KS. A wide spectrum of drugs was confirmed to be suspected triggers for KS, including NSAIDs, antibiotics and anesthetics (non-depolarizing curares or alogenates). According to the author, serum tryptase is far to be accepted as indicator or diagnostic criteria for KS and this data was never reported in the 51 reports of our case series.

The treatment of KS should counteract both the allergic and the cardiac symptoms: corticosteroids with H₁ and H₂ antihistamines are useful. Drugs used for cardiac symptoms could worsen the clinical picture: vasodilators such as nitroglycerin or Ca Channel blockers can reverse the coronary spasm but could induce hypotension and tachycardia. Adrenaline was reported as a life-saving drug to improve hemodynamic stability during allergic reactions and is a first choice drug that can save lives in anaphylaxis [10] but it also increases the myocardial oxygen consumption and some authors suggest that its use should be restricted to life-threatening cases as a last resource [3]; the use of sulphite free adrenaline was suggested in severe cases [9]. Actually, there is no clear guidelines for the management of KS, but some authors have started to collect suggestions and recommendations about treatment of cardiac and allergic symptoms [3,12].

Recently some cases [24] reporting the association between Kounis and Takotsubo syndrome, an acute cardiac syndrome with usually normal coronaries triggered by a mental stress condition (such as a surgical procedure), led to an interesting debate in literature [25,26]. In our analysis, we found five cases of KS in the perioperative setting and this could suggest a potential common link in the pathogenesis of these two cardiac syndromes (KS and Takotsubo), with a difficult differential diagnosis.

In our case series we found only one metal (nickel) allergy. Since there are many patients treated with metal coronary stents it could be expected to find several reports of KS in stented patients. Even if few case reports of KS after metal coronary stent implantation exist in

literature, we speculate that it is possible that these ischemia episodes are often attributed to peripheral coronary disease and not to KS.

Interestingly, some cases of “Kounis like syndrome” involved cerebral [27,28] and mesenteric vessels [29]. These cases could lead to an evolving concept of KS from a “cardiac specific” to a “systemic clinical condition”.

4.3. Strengths and limitations

Our study is the largest case series ever published on KS, and the first based on analysis of reports in international pharmacovigilance database. Nonetheless all cases included are from spontaneous reporting and are probably the tip of the iceberg since clinicians in their daily activity seldom report adverse drug-related events and under-reporting is a peculiar limitation of the spontaneous reporting system. Our study has several limitations. First, the narrative detailed reports were available only for European cases. Second, the lack of medical history was an important missing information. Third, with the available data from spontaneous reports we were not able to establish if the most frequently reported substances (eg NSAIDs, cardiovascular drugs and antibiotics) have an association with this syndrome or if they're simply more prescribed than other drugs. Fourth, the pharmacovigilance reports did not have enough data to differentiate between different types of Kounis Syndrome. Fifth, we identified only the pharmacovigilance reports that referred “Kounis Syndrome” as a preferred term to describe the adverse reaction and might have missed several cases that reported terms as “eosinophilic reaction”, “allergic reaction”, or “hypersensitive reaction”; at the same time we reduced confounders and over diagnoses. Sixth, data came from the VigiBase® database and are not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse event.

4.4. Study implications

Our analysis showed that recently the diagnosis of Kounis Syndrome is increasing in the international pharmacovigilance reports. These data should suggest a concurrent increasing awareness about KS by clinicians. KS could have an important role in the differential diagnosis of acute cardiac ischemic events.

5. Conclusions

We showed an increasingly reporting of KS cases, especially in the last year. NSAIDs, cardiovascular and antibiotics were the most frequently involved drugs, but for the rarity of cases and few information it is not possible to establish a causal relation with the occurrence of KS. We suggest to consider KS in the differential diagnosis of ischemic heart diseases.

Disclosures

All the authors have nothing to disclose

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Appendix A. Supplementary data

Caveat document: Accompanying statement to data released from the Uppsala Monitoring Centre, WHO Collaborating Centre for

International Drug Monitoring. Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijcard.2015.10.003>.

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CAVEAT DOCUMENT

Accompanying statement to data released from the WHO Collaborating Centre

The WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden receives summary clinical reports about individual suspected adverse reactions to pharmaceutical products from National Centres in countries participating in a Collaborative Programme. Only limited details about each suspected adverse reaction are received at the Centre. It is important that the limitations and qualifications which apply to the information and its use are understood.

The term "pharmaceutical product" is used instead of "drug" to emphasize that products marketed under one generic or trade name may vary in their content of active or other ingredients, both in time or from place to place.

The reports submitted to the Collaborating Centre in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a pharmaceutical product or ingredient is the cause of an event.

The reports, which are submitted to National Centres, come from both regulatory and voluntary sources. Some national Centres accept reports only from medical practitioners; other National Centres accept reports from a wider spectrum of health professionals. Some National Centres include reports from pharmaceutical companies in the information submitted to the Collaborating Centre; other National Centres do not.

The volume of reports for a particular pharmaceutical product may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time, from product to product and country to country. Moreover, no information is provided on the number of patients exposed to the product.

Thus the sources of reports accepted by National Centres vary, as do the proportions.

A number of National Centres which contribute information to the Collaborating Centre make an assessment of the likelihood that a pharmaceutical product caused the suspected reaction. Other National Centres do not document such assessments on individual reports in the WHO data base.

Processing time varies from country to country. Reporting figures obtained from the Collaborating Centre may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between pharmaceutical products, may be misleading. The information tabulated in the accompanying printouts is not homogeneous with respect to the sources of the information or the likelihood that the pharmaceutical product caused the suspected adverse reaction. Some describe such information as "raw data". Any use of this information must take into account at least the above.

Some National Centres which have authorized release of their information strongly recommend that anyone who intends to use it should contact them for interpretation.

Any publication, in whole or in part, of the obtained information must have published with it a statement:

- (i) of the source of the information,
- (ii) that the information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction,
- (iii) that the information does not represent the opinion of the World Health Organization.

Omission of these 3 statements may exclude the responsible person or organization from further information from the system.