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Kounis syndrome due to antibiotics: A global overview from pharmacovigilance databases

Francesca Renda [a], Elena Marotta [a], Giovanni Landoni [b,c,*], Alessandro Belletti [b], Virginia Cuconato [a], Luca Pani [a]

[a] Italian Medicines Agency, Rome, Italy
[b] Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy
[c] Vita-Salute San Raffaele University, Milan, Italy

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ABSTRACT

Background: Kounis syndrome (KS) is characterized by concurrent presence of anaphylactic and cardiac components. Available evidence suggests that antibiotics are frequently associated to KS. We therefore analyzed KS cases associated with antibiotics use from the two largest pharmacovigilance databases.
Methods: Two pharmacovigilance databases, EudraVigilance and VigiLyze, were searched for cases reporting the adverse reaction "Kounis Syndrome" with antibiotics as suspected active substance. We analyzed the period from December 1st, 2001 to February 16th, 2016. For the most reported active substance, proportional reporting ratio (PRR) was calculated.
Results: A total of 10 cases of KS associated with antibiotic use were retrieved from EudraVigilance database. Mean patients' age was 58.2 years and 70% were male. The most frequently reported suspected antibiotic was the combination amoxicillin/clavulanic acid (four cases). VigiLyze database reported 13 KS cases associated to antibiotics. Mean age was 56 years and 61% of patients were male. The most frequently reported antibiotic was again the combination amoxicillin/clavulanic acid (five cases). Seven duplicate cases were identified, leaving a total of 16 cases of KS, with six of them associated to amoxicillin/clavulanic acid use. The PRR value for amoxicillin/clavulanic acid against other kinds of antibiotics was 2.62 considering EudraVigilance data and 1.61 considering VigiLyze data.
Conclusions: This analysis provided a complete picture of the cases of KS associated with antibiotic use and identified a possible association between amoxicillin/clavulanic acid and KS. Since the number of cases is low, especially considering its wide use, further analyses are needed to confirm the association.

1. Introduction

Kounis syndrome (KS) is a recently described disease characterized by the concurrent presence of anaphylactic and cardiac components [1]. Following an allergic stimulus, the activation of mast cells leads to histamine, leukotrienes and serotonin release [2]. In severe cases, these mediators can trigger a massive hemodynamic response with generalized vasodilatation leading to allergic or anaphylactic shock. In KS, inflammatory mediators cause a spastic contraction of coronary smooth muscle cells [3]. Mast cells [4], eosinophils and lymphocytes [5] are usually found in histological reports. However, the exact pathophysiologic mechanism underlying this syndrome remains unclear. The syndrome usually manifests clinically with typical cardiac ischemic signs and symptoms such as chest pain, electrocardiographic alterations in ST segment or T waves, or atrioventricular block and other arrhythmias. Cases of myocardial infarction (MI) with elevation of myocardial necrosis biomarkers have also been observed [6]. Clinical findings suggestive of an allergic or hypersensitivity reaction, such as hypotension, pruritus or dyspnea, complete the typical presentation of the syndrome [1]. This syndrome might also result in death, usually by complications of MI [7].

Kounis syndrome can occur in elderly as well as in pediatric age [8,9]. There is currently no consensus on the best treatment of KS [10] and therapy is directed on one side to reduce the inflammatory cascade and allergic reaction by administration of corticosteroids and antihistamines and on the other side to manage the acute coronary syndrome [6]. The use of adrenaline is debated since it is the drug of choice in the case of severe allergic reactions [11,12] but have well-known side effects which may worsen a ventricular function already compromised by ischemia [10,13,14]. However, it has been frequently given to patient with KS and should be considered as treatment of the most severe cases [15].

Potentially, any kind of medication can trigger severe allergic reactions and multiple agents were associated with KS, although antibiotics are the most frequently involved drugs [16,17]. Insect bites [18–20] and drug-eluting stents [21,22] have also been associated with KS.

Actual incidence of KS is yet to be determined. However, despite the rarity of KS, there is an increasing awareness of physicians on this

* Corresponding author at: Department of Anaesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy.
E-mail address: landoni.giovanni@hsr.it (G. Landoni).

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specific event, in particular when KS occurs following the use of medicines. We recently reported a large case series of pharmacovigilance-reported cases of KS [23] that confirmed that antibiotics are among the drugs most frequently associated with KS. Therefore, aim of our study was to identify and describe KS cases associated to antibiotic administration by searching two large pharmacovigilance databases, and to analyze causing drugs, clinical presentation of KS, and treatment undertaken to manage the syndrome.

2. Methods

Two pharmacovigilance databases, EudraVigilance and VigiLyze, were searched. The EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse drug reactions (ADR) during the development and the marketing authorization of medicinal products in the European Economic Area (EEA). The first operating version was launched in December 2001. VigiLyze is the global World Health Organization database for Individual Case Safety Reports (ICSRs) spontaneously collected since 1968, and includes data from over 100 countries (including U.S. and Europe). It is managed by the Uppsala Monitoring Centre on behalf of the World Health Organization.

We collected all cases that reported the ADR "Kounis Syndrome", preferred term based on Medical Dictionary for Regulatory Activities (MedDRA) [24], associated to the antibiotics when these were considered suspected active substance by the reporter. A case by case analysis was conducted from three expert investigators who carefully excluded all reports already published in scientific literature and duplicated cases from both databases. Antibiotics were included based on anatomical therapeutic chemical (ATC) classification "J01–antibacterials for systemic use". We investigated cases reported between December 1st, 2001 and February 16th, 2016.

The following variables were extracted from the identified reports: geographic region, year of ADR occurrence, age, sex, type of ADR, time to ADR onset, seriousness and clinical outcome, suspected causative drug, concomitant drugs and their therapeutic indications, route of administration, type of reporter. Also the narrative of the cases was analyzed if available; thus, an in-depth analysis aimed at identifying underlying risk factors, features of symptomatology, clinical procedures to confirm the diagnosis of KS, and actions undertaken to manage the event, was performed.

The proportional reporting ratio (PRR) was calculated taking into account the cases of KS associated with amoxicillin/clavulanic acid, the substance most frequently associated with KS among antibiotics, for the period 2001–2016. The PRR summarizes the strength of the association between an ADR and a drug and it is applicable with a minimum of three cases. It compares the frequency of a particular ADR (in individuals taking a specific drug) with the frequency with which the same adverse event occurs in patients taking all other drugs. We computed PRR as described by Evans et al. [25] (Supplementary Appendix). To calculate PRR, we considered all reports of KS available from databases (comprehensive of literature cases) for amoxicillin/clavulanic acid, for other active substances and for antibiotics involved in KS (amoxicillin, amoxicillin/clavulanic acid and its salts, ceftriaxone, piperacillin/tazobactam, cefazolin, levofloxacin, metronidazole). In particular, we calculated PRR also comparing cases of ADRs associated with amoxicillin/clavulanic acid both versus cases of ADRs associated with all other drugs and versus cases of ADRs associated with all other antibiotics. Of note, due to organization of the pharmacovigilance databases and the large number of cases reported, it was very difficult to identify and exclude duplicate and previously published cases of KS and other adverse reactions to antibiotics and all the other drugs. Therefore, for consistency purposes, we decided not to exclude duplicate and already published KS cases, in order to not introduce a bias in the PRR calculation. As a result, PRR was calculated including all cases of KS registered in the databases, including duplicate and previously published cases.

Ninety-five percent confidence interval (95% CI), chi-squared and standard deviation were also calculated.

After identification of all cases, we cross-checked the data from the two databases in order to identify and delete duplicated cases. Duplicated cases were identified following in-depth analysis of the data on geographic area, age, gender, described ADR and suspected drug. Also the data on seriousness and the outcome more described than others were reported.

The causality assessment was performed on the cases KS and amoxicillin/clavulanic acid using the Naranjo algorithm [26] for standardized case causality assessment. Causality assessment, as performed by three expert operators, allowed to evaluate and classify causal relationship between drug intake and onset of adverse drug reaction as definite, possible, probable or doubtful.

3. Results

3.1. EudraVigilance cases

In the considered period, 10 cases of KS associated to antibiotic use were retrieved (Table 1). The first two spontaneous reports were registered in 2012, followed by four cases reported in 2014 and further four in 2015.

Table 1
Spontaneous reports of Kounis Syndrome retrieved in EudraVigilance and Vigylize.

	EudraVigilance (N)	Vigylize (N)
Geographic region		
US	0	2
Europe	10	11
Sex		
Male	7	9
Female	3	4
Not specified	0	0
Age groups		
1–17 years	1	1
18–65 years	6	8
65 + years	3	4
Active substance		
Amoxicillin/clavulanic acid	4	5
Amoxicillin	2	3
Piperacillin/tazobactam	2	2
Others (levofloxacin, metronidazole, cefazolin, ceftriaxone)	2	3
Seriousness		
Caused/prolonged hospitalization	2	4
Death	0	0
Life threatening	3	3
Life threatening, caused/prolonged hospitalization	3	4
Not available	1	2
Outcome		
Fatal	0	0
Not recovered/not resolved	0	0
Recovering/resolving/resolved/resolved with sequelae	10	11
Unknown	0	2
TOT cases	10	13

These ten cases occurred in France (3 cases), Liechtenstein (2 cases), Italy (2 cases), Turkey, Spain and the Netherlands (1 case each). All ten cases were reported by health care professionals. Mean age was 58 years old (range 14–99) and males were 70% (seven cases). All cases were reported from healthcare professionals. The most frequently reported suspected active substances were the combination amoxicillin/clavulanic acid (4 cases) followed by amoxicillin (2), piperacillin/tazobactam (2), ceftriaxone (1) and cefazolin (1).

In three cases an antibiotic monotherapy was described: amoxicillin, piperacillin/tazobactam and ceftriaxone. Concomitant medications were reported in 7 seven cases and ranged from two to five drugs. Narratives of the cases described the following concomitant drugs: paracetamol (1 case); propofol, cisatracurium, sufentanil (1 case); gliclazide, paracetamol, sitagliptin, simvastatin, hydroxyzine (1 case); lactic acid bacteria (1); acetylsalicylic acid, atorvastatin (1 case); acetylsalicylic acid, clopidogrel, diltiazem hydrochloride, ramipril, atorvastatin (1 case); perindopril (1 case).

Information about indication for antibiotic therapy was available for nine cases. Kounis syndrome developed in two patients receiving antibiotic as prophylaxis before surgical procedures, in two patients receiving antibiotics for treatment of erysipelas, in two patient receiving antibiotics for dental care and in one patient each who was receiving antibiotics for sore throat, for prevention (not otherwise specified) and for automedication for cough.

The route of administration was reported in nine cases: intravenous administration in five cases and oral administration in four cases.

Kounis syndrome was confirmed by electrocardiograms (2 cases) and laboratory examinations (5 cases), including triptase (2 cases), eosinophiles count (1 case) and troponin (3 cases) samplings. Prick test for amoxicillin was performed in one patient and had positive results.

Three patients had a history of hypersensitivity (3 cases) and three patients had a history of cardiovascular disease (myocardial ischaemia, peripheral arterial occlusive disease; aortic valve insufficiency, hypertension; myocardial ischaemia, respectively).