Drug-induced Kounis Syndrome: A Retrospective Pharmacovigilance Study from the FAERS and JADER Databases

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Kounis syndrome (KS) is defined as an acute coronary syndrome that occurs in association with an allergic reaction [1]. Its pathophysiology is linked to the activation of mast cells and platelets [2]. According to current research, the etiology of KS includes various triggers, such as drugs, vaccines, foods, disease, and environmental exposure, with drugs being one of the primary instigators [2-4]. A broad spectrum of drugs, ranging from over-the-counter medications to specialized prescription drugs, has been implicated in KS, with antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) being the most frequently involved [5]. Given the associated diagnostic challenges and limited clinical awareness of this condition, KS is often misdiagnosed or underdiagnosed.

Prevention and early diagnosis of KS are of paramount importance, as severe allergic reactions and acute coronary syndromes are potentially life-threatening. We conducted a signal mining study across large data sets from the FAERS and JADER databases to identify drugs that carry a high potential risk of inducing KS.

The United States Food and Drug Administration has made the FAERS database publicly accessible since the first quarter of 2004. FAERS contains a total of 53 715 275 adverse event reports [6]. Similarly, Japan's Pharmaceuticals and Medical Devices Agency has provided access to the JADER database, which contains 1 471 028 adverse event reports from the first quarter of 2004 [7]. This study utilized data from both the FAERS and JADER databases from the first quarter of 2004 to the first quarter of 2024, including 3 subdatabases (DEMO, REAC, and DEMO), which provide detailed information on population characteristics, adverse events, and drug usage. To enhance the study's reliability, we preprocessed the data obtained initially from both databases (Figure S1). We then summarized the clinical characteristics of populations with drug-related KS in each database, analyzing factors such as sex, age group, and country. Disproportionality analysis was performed by calculating the reporting odds ratio (ROR) and its 95%CI for the top 40 drugs in the FAERS database and the top 30 drugs in the JADER database (Table S1). A drug was classified as a potential risk if its signal strength met the criteria established by the ROR algorithm.

We identified 1637 cases in the FAERS database and 186 cases in the JADER database, where drugs were the primary suspects for causing KS between the first quarters of 2004 and 2024. In the FAERS database, 33.11% of the cases were female, 59.01% were male, and the sex was unknown in 7.88% of cases. The largest age group was 40-59 years (29.69%), with 0-19 years representing 4.28% of cases (Table S2). The most frequently reported drugs were amoxicillin, diclofenac, and ibuprofen. In the JADER database, 26.88% of cases were female, and 72.58% were male, with sex unknown in 1 case. Patients aged 60-79 years accounted for 59.68% of the cases, and the top 3 drugs reported were fentanyl, iopamidol, and propofol (Table S3).

The ROR values for the top 40 drugs in the FAERS database ranged from 2.61 to 129.78, with sugammadex showing the highest risk signal. In the JADER database, the ROR values for the top 30 drugs ranged from 0.90 to 86.94, with sugammadex again displaying the highest signal (Figure S2). Cases involving males (n=966) and females (n=542) were extracted separately from the FAERS database, revealing 32 potential risk drugs in the male subgroup and 30 in the female subgroup. Sugammadex demonstrated the highest signal strength in both subgroups. Similarly, in the JADER database, cases involving males (n=135) and females (n=50) were analyzed, identifying 19 potential risk drugs in males and 12 in females. In the male subgroup, sugammadex had the highest signal strength, while in the female subgroup, the highest signal was recorded for desflurane (Figure S2).

Sugammadex emerged as the drug with the highest ROR in both databases, and its concurrent use with rocuronium, another drug with a high ranking, raised significant concerns. The high affinity of sugammadex for rocuronium compared to other neuromuscular blocking agents has led to the combination being used increasingly frequently in anesthesia [8]. A study conducted from September 2018 to August 2019 found that the incidence of suspected perioperative allergic reactions in China was 1/11 360, with a notable increase from north to south [9]. Current case reports suggest that sugammadex, rocuronium, and the rocuronium-sugammadex complex all have the potential to induce KS [10-12]. Therefore, both sugammadex and rocuronium warrant close monitoring as significant risk factors for KS.

Our analysis also highlighted antibiotics as a class of drugs with considerable potential risk. Cefuroxime, in particular, had the highest ROR among antibiotics in the FAERS database. The earliest recorded case of drug-induced KS, reported in

1950, was attributed to penicillin [13]. Notably, the antibiotics identified as potential risks in the FAERS and JADER databases were not entirely consistent, probably because of differences in the range of antibiotics approved in different regions or countries. For example, cefcapene pivoxil was introduced in Japan in 1997 but is not marketed in the US or Europe. Its primary market continues to be Japan and a few other Asian countries.

Multiple contrast agents were associated with potential risks in both the FAERS and the JADER databases. However, the specific agents at risk varied between the 2 databases, likely reflecting regional differences in the choice of agents for imaging examinations. For instance, iopromide and iohexol are widely used in both the US and Japan, while iomeprol is more commonly used in Japan and less so in the US. Consequently, targeted drug monitoring based on real-world conditions in different regions and countries is necessary.

In conclusion, this study identified sugammadex and rocuronium as carrying a significant potential risk for inducing KS. Additionally, contrast agents, antibiotics, antineoplastic agents, and NSAIDs were the main classes of drugs associated with KS. Given the heterogeneity of data sources and regional differences in drug usage, targeted drug monitoring is crucial. Further research is required to establish a definitive causal relationship between drug administration and KS, considering the biases inherent in observational data and the complexities of accurately diagnosing this syndrome.

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The links to the original data used in this study are clearly indicated in references 6 and 7. The R software code used to complete the study can be obtained by contacting the corresponding author.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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