2022

Colistin-associated Stevens-Johnson syndrome and toxic epidermal necrolysis reactions: a retrospective case-non-case pharmacovigilance study

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ORIGINAL ARTICLE

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1. Abstract (count 198)

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening skin reactions. Colistin is a last resort antibiotic with a historically poor safety profile. The association between colistin and SJS/TEN has not been previously quantified.

Methods: We identified colistin and SJS/TEN adverse event reports from the Food and Drug Administration Adverse Event Reporting System (FAERS) and calculated effect estimates using OpenEpi.

Results: From January 2013 through March 2021, 964 adverse events were reported for colistin. Colistin was listed as a secondary suspect drug in 13 SJS/TEN adverse event reports (1.3%), with a reporting odds ratio of 29.6 (95% confidence interval [CI] 17.1-51.1), and proportional reporting ratio of 29.2 (95% CI 17.0-50.2).

Limitations: The limitations that accompany any FAERS study include the voluntary nature of reporting, unclear causal relationship between drug and adverse reaction, underreporting, and wide confidence intervals for rare adverse events like SJS/TEN.

Conclusion: Colistin was not the primary suspect drug in any SJS/TEN adverse event reports. We did identify a statistically significant safety signal for SJS/TEN with colistin as a secondary suspect drug. SJS/TEN is not currently included in the colistin product label. This association should be further explored in other pharmacoepidemiologic drug safety studies.

Manuscript text (word count 2,942)

3.1 Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both rare and life-threatening skin reactions that can occur as an adverse event due to a medication or as a result of an infection. The distinction between the two conditions is that SJS is defined as skin involvement of <10% of total body surface area (TBSA) whereas TEN is defined as >30% of TBSA skin involvement. Skin involvement between the ranges of 10-30% are considered SJS/TEN overlap.[1] For the purpose of this study, all SJS or TEN reactions will be referred to as SJS/TEN. The cause of this reaction revolves around an immune complex mediated type-IV, subtype c, hypersensitivity reaction involving T-cells.[2] This hypersensitivity has been associated with certain classes of medications and possibly certain infections as well. Medications associated with SJS/TEN include, but are not limited to, certain anticonvulsants, certain nonsteroidal anti-inflammatory medications (NSAIDs), allopurinol, and certain antibiotics, including sulfonamides, penicillins, and cephalosporins.[3-5] Non-medication related SJS/TEN reactions have been implicated in literature as well, suggesting that certain infections, such as human immunodeficiency virus (HIV) and *Mycoplasma pneumoniae*, increase the risk of developing SJS/TEN.[3, 6]

SJS/TEN reactions are life threatening conditions with SJS mortality rates ranging from 5% up to 30%.[7] The disease causes skin detachment and water loss which can lead to acute complications including infections of the skin, pneumonia, and septicemia as well as dehydration, acute malnutrition, and multiple organ failure.[8] In addition to these well-defined acute complications, SJS/TEN is now recognized to cause long term complications even after initial resolution. Long-term sequelae include ocular, mucocutaneous, respiratory, gastrointestinal tract, and psychological complications which ultimately impacts a patient's quality of life. [9, 10]

Colistin is a last resort antibiotic with a historically poor safety profile. The antibiotic belongs to the polymyxin class in which each chemical compound is differentiated by their amino acid sequences and fatty acid side chains. The two primary polymyxins used in clinical practice include polymyxin B and polymyxin E (colistin).[11] Colistin is chiefly effective against strains of gram-negative bacilli such as *Pseudomonas aeruginosa, Enterobacter aerogenes, Escherichia coli,* and *Klebsiella pneumoniae* that are resistant to other antibiotics. Off label indications include a nebulized form of colistin for bronchiectasis in both cystic fibrosis (CF) and non-cystic fibrosis patients and hospital-acquired or ventilator-associated pneumonia.[12] Previous pharmacovigilance studies using the Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS), as well as other health outcomes

studies, have demonstrated a strong association between colistin and nephrotoxicity especially with increasing cumulative doses of colistin. Colistin, as well as polymyxin B, have both been reintroduced into the antimicrobial armory as multidrug-resistant bacteria are becoming both more prevalent and difficult to treat.[11-14] Due to the known toxicity of colistin and increased risk of SJS/TEN with other antibiotics[1,3-6], we investigated SJS/TEN reporting rates with colistin utilizing FAERS data in this case-non-case study, a study design used specifically to analyze the disproportionality of drug safety events in pharmacovigilance databases.

3.2 Methods

In this retrospective case-non-case study, we analyzed adverse event reports from the FAERS data for the period of January 2013 through March 2021 (analysis date August 2021). Case-non-case studies compares cases of an adverse reaction of interest, in this case SJS/TEN, compared to all other reported reactions, considered non-cases. The FAERS database contains reports of adverse events from the FDA's post-marketing safety surveillance program and is freely accessible to the public. Ethics approval was not required, as the study utilized a publicly available data source that does not contain any identifiable information. Adverse events are coded under Medical Dictionary for Regulatory Activities (MedDRA) terms, and we included the MedDRA terms Stevens-Johnson syndrome, toxic epidermal necrolysis, and SJS-TEN overlap[15] While manufacturers are mandated by law to report certain adverse events to FAERS, healthcare professionals and patients themselves are able to voluntarily submit adverse event reports to FAERS. [16]

We excluded duplicate reports from the analysis, as well as follow-up reports, and reports missing date, gender, or age. Broad search terms were used to identify reports with the antibiotic of interest, colistin, either as a primary or secondary suspect drug. Multiple forms and brands of colistin were referenced from DrugBank and utilized in our search.[17] The following drug names were included: colistin, colimycine, colistimethate, colomycin, coly-mycin. A secondary analysis evaluating polymyxin B and SJS/TEN reactions was conducted. We compared age, type of reaction, and sex between colistin reports with all other reports, using a t-test, Chi-square test, or Fisher's Exact test as appropriate. We also assessed time to onset, other adverse events, outcomes, as well as all primary and secondary suspect drugs for colistin and SJS/TEN reports. Reporting odds ratio (ROR), proportional reporting ratio (PRR), and corresponding 95% confidence intervals (CIs) were calculated for SJS/TEN reactions

with colistin and polymyxin B, as compared with all other medications, using OpenEpi (version 3.01).[18] ROR and PRR confidence intervals which did not contain 1.0 were considered statistically significant.

3.3 Results

Over the study period of January 2013 through March 2021, there were a total of 8,102,577 adverse event reports, and 0.03% (n=3,760) listed SJS/TEN reactions, with 13 of those reports listing colistin as a secondary suspect drug (0.3%; 1 report listed polymyxin B, 0.03%). Patients with SJS/TEN reports listing colistin as a secondary suspect drug were significantly younger than SJS/TEN reports listing other drugs (mean age 38.5 versus 51.7, p=0.04), and more commonly male (84.6% versus 44.1%, p=0.01; Table 1). Most reports were cases of SJS for both colistin (92.3%) and other drugs (61.2%).

For the 13 adverse event reports of SJS/TEN listing colistin, Table 2 describes the primary and secondary suspect drugs from those reports, as well as the time to onset of SJS/TEN, co-occurring adverse events, and clinical outcomes. Colistin was a secondary suspect drug in all reports, and 11 other medications were listed as primary suspect drugs, 6 (54.5%) of which were antibiotics, antivirals, or antifungals. The mean time to onset was 10.6 days (standard deviation 2.6 days; median of 11 days, interquartile range 10-13 days).

Co-occurring adverse events included 8 (61.5%) with other skin problems, 2 (15.4%) with multiple-organ failure, 4 (30.8%) with pancytopenia, and 5 (38.5%) with no other adverse events. None of the report listed nephrotoxicity, impaired renal function, or renal failure. Outcomes for 12 of the 13 cases were recorded, which included 6 (46.2%) patients who died and 6 (46.2%) were listed as life-threatening. The most common other secondary suspect drugs (n=38) included amphotericin B (n=12, 92.4%), ciprofloxacin (n=11, 84.6%), esomeprazole (n=9, 69.2%), fluconazole (n=8, 61.5%), and teicoplanin (n=7, 53.8%).

Colistin had a statistically significant ROR of 29.6 (95% CI 17.1-51.1) and a statistically significant PRR of 29.2 (95% CI 17.0-50.2; Table 3) as a secondary suspect drug for SJS/TEN. There were 89 adverse event reports for polymyxin B with one (1.1%) report of SJS/TEN, resulting in a statistically significant ROR of 24.7 (95% CI 3.4-176.4) and statistically significant PRR of 24.3 (95% CI 3.4-170.7).

3.4 Discussion

The results of our study with recent FAERS data show that colistin was not listed as a primary suspect drug for any SJS/TEN adverse event reports, and therefore this association could not be assessed. When evaluating SJS/TEN adverse event reports where colistin was listed as a secondary suspect drug, reporting rates were almost 30 times higher compared with all other drugs. Existing literature does not mention any association between SJS/TEN and colistin. Further, this reaction is not listed in colistin package inserts. [19-22] A similar association was observed with polymyxin B, a 25 times higher reporting rate than other drugs. However, there was only one report of SJS/TEN and polymyxin B, resulting in a wide confidence interval which limits any conclusions which can be made from this finding.

Though colistin was not the primary suspect drug in any of the 13 SJS/TEN reports, 85% of report had a different primary suspect drug. The secondary suspect drug list consisted of 39 unique drugs, including antibiotics, antivirals, antifungals, proton pump inhibitors or 5-HT3 antagonists. Interestingly, no antiepileptics were listed as primary or secondary suspect drugs among the 13 reports. The most common secondary suspect drugs were amphotericin B (n=12, 92.4%) and ciprofloxacin (n=11, 84.6%), which both include warnings about SJS/TEN reactions in their package inserts [23,24]. Many of the secondary suspect drugs have also been identified as increasing the risk of SJS/TEN using the algorithm of drug causality for epidermal necrolysis (ALDEN). As colistin is used in combination with other drugs associated with SJS/TEN, it is not possible to study the drug safety of colistin alone in observational studies. However, it is important to note the possibility that certain combinations of antibiotics, or antibiotics and antifungals, may increase the risk of SJS/TEN compared with administration of those therapies alone. It will be important for future studies to assess risk of SJS/TEN in the context of combination therapies, relative to the risk of these therapies alone or in other combinations. Such studies would need to assess the incidence of SJS/TEN in patients with serious infections receiving antibiotic regimens which include colistin versus the same/similar regimens without colistin.

Studies have shown with allopurinol and its active metabolite oxipurinol that prior impaired renal function can increase the severity of skin reactions such as SJS/TEN [25]. As nephrotoxicity is a well-recognized drug safety issue with colistin, nephrotoxic effects could impact the risk and severity of SJS/TEN reactions due colistin itself, or due to co-administered drugs which carry the risk of SJS/TEN, including amphotericin B and ciprofloxacin. However, nephrotoxicity, or impaired renal function, were not listed as other adverse events in any of the SJS/TEN adverse event reports, limiting the assessment of these effects.

The Weber effect states that adverse event reporting for a drug is at its highest for the first two years post-marketing approval and begins to drop off thereafter. Interestingly, colistin has been in use clinically for roughly 60 years and still has significant reporting rates for SJS/TEN in the recent FAERS data analyzed.[25] One explanation is that a decline in reporting may occur mainly with clinically mild adverse events, while more serious events are consistently reported year to year.[26] Further, since the Weber effect was first described in 1984, adverse event reporting systems have been modernized, and are now more accessible and streamlined, leading to greater adverse event reporting.[27] Although there is conflicting evidence on the continued validity of the Weber effect, some studies have found that the Weber effect is outdated and may not apply to current day adverse event reporting systems.[27-30]

Although colistin has been used for around 60 years, its time on the market should not discredit new safety signals. FAERS has been shown to identify previously unknown reactions, even for older medications that have been on the market for decades. Among 233 signals identified from FAERS between 2008 and 2014, most safety signal were associated with newer drugs on the market for less than 5 years (76, 32.6%), however some signals were identified for drugs on the market for 20 years or more (63, 27.0%).[31] One of these signals was mercaptopurine-associated hepatosplenic T-cell lymphoma (HSTCL). Mercaptopurine was in use for 57 years at the time of signal detection and the newly recognized adverse event led to product labeling updates.[32, 33] Similarly, conjugated estrogens were in use for 67 years at the time of signal detection for angioedema, that led to labeling changes.[34]

SJS/TEN is a rare condition, with an estimated annual incidence rate of 1 to 5 cases in 1,000,000 individuals, with even higher rates in adults 65 and older which may be due to higher rates of medication use in older populations.[35-40] The average age for the SJS/TEN reports with colistin as a secondary suspect drug was 38.5 years old. These younger cases may represent a particular patient population at risk of serious infection, such as individuals with CF, who are frequently treated with multiple antibiotics/antifungals and therefore represent an at-risk population if there exists a greater risk of SJS/TEN due to combinations of medications associated with SJS/TEN [13]. FAERS is an effective data source for adverse event signal detection, particularly for rare outcomes and rare exposures, meaning rare adverse events, such as SJS/TEN, and last-line therapies with limited use, such as colistin. Even in very large observational studies (e.g. 10 million individuals or more), there may be too few events to detect an association with any specific medication, especially one that is less commonly used. FAERS, however,

has been able to detect safety signals for very rare adverse events, for example, mercaptopurine-related HSTCL as the estimated annual incidence of HSTCL is only 0.3 per million person-years. [29, 30, 32, 38]

The main concerns for colistin associated adverse reactions include nephrotoxicity, neurotoxicity, and respiratory arrest, most of which are dose dependent.[19-22] A previous FAERS study investigated the most common antibiotics associated with acute kidney injury (AKI) from 2015 through 2017. They reported that colistin had the greatest proportion of AKI reports, with a statistically significant ROR of 33.10 (CI 21.24-51.56), representing nearly 25% of all colistin reports. The study also highlighted the fact that previous studies of AKI reactions have only included medications with the greatest total number of AKI reports, which ultimately excluded colistin due to its limited use and corresponding lower number of total reports.[13]

Due to colistin's well-known adverse effect profile in terms of nephrotoxicity and neurotoxicity, it is important to consider the possibility that certain adverse effects with colistin may be masked by other drugs previously shown to be associated with SJS/TEN, such as penicillin, antiepileptics, antipyretics, analgesics, and/or the infection itself. This may explain why colistin was recorded as a secondary suspect drug in all 13 reports of SJS/TEN instead of a primary suspect drug. Due to the fact that colistin is often used with other antibiotics, antivirals, antifungals, and other supportive medications that have been associated with SJS/TEN, the reaction is more likely to be attributed to those medications with such established risk.

Masking has led to missed signal detection, as evidence from a systemic masking analysis using the EudraVigilance database of the European Medicines Agency.[42] In this study, ceftriaxone was identified as the drug with the highest masking effect for anaphylactic shock due to its disproportionate amount of reports. After removal of ceftriaxone reports, they unmasked an association of fusafungine with anaphylactic shock. This masked safety signal was detected three years prior to standard signal detection, which eventually led to regulatory action and market withdrawal. This may explain why colistin was recorded as a secondary suspect drug in all 13 reports of SJS/TEN instead of a primary suspect drug. Another important aspect of masking to consider is intra-drug masking or event-competition bias, where disproportionately reported adverse events for a drug can hide other safety concerns for that same drug. This was observed with statins when reports of commonly reported rhabdomyolysis/myopathy were removed from a French pharmacovigilance research database (1986 to 2001) and 11 new signals of disproportionate reporting were identified.[43] Similarly, colistin signals may have been masked due to its disproportionately reported adverse events of nephrotoxicity (n=40, 7.2%).

The limitations of this study relate to the data source and therefore affect all studies utilizing FAERS data. Though these limitations are previously well-described and clearly explained on the FAERS website, [16,44-48] in summary they include (1) the voluntary nature of reporting, (2) hence the reports do not represent estimates of the incidence nor prevalence of adverse reactions with the medications of interest, (3) a low threshold for relatedness of the reaction to the medication (e.g. no requirement that the relationship be clearly causal or that reports utilize ALDEN), (4) missing data, (5) misclassification of medications and/or reactions, (6) underreporting, (7) low adverse report counts for rare events leading to wide confidence intervals, and (8) confounding by co-medications which may or may not (missing data) be included in the report. Patients being treated with colistin are likely also being treated with other antibiotics, as well as supportive care medications such as antipyretics or analgesics which have been linked to causing SJS/TEN, as demonstrated with the 11 primary suspect drugs and 39 secondary suspect drugs.[49,50] As such, these medications may themselves have been responsible for the SJS/TEN reaction, either alone or in combination with colistin or other medications. Due to the low number of SJS/TEN reports with colistin as a secondary suspect drug (n=13), we observed a wide confidence interval. However, even at the low end of the confidence interval, the reporting rates for SJS/TEN with colistin as a secondary suspect drug was nearly 10 times higher than with other medications, indicating a potential safety signal.

3.5 Conclusions

In our pharmacovigilance disproportionality analysis, colistin was not listed as a primary suspect drug for any SJS/TEN adverse event reports, and therefore this association could not be assessed. We did identify a statistically significant safety signal for SJS/TEN with colistin as a secondary suspect drug, where reporting rates were 30 times higher compared with all other medications. SJS/TEN is not currently included in the colistin product label. Evidence of this safety signal should be assessed further in other pharmacoepidemiologic drug safety studies and among other study populations. While the use of a pharmacovigilance database such as FAERS is a reasonable first step in the signal detection process, in this particular case, the database did not have any cases of SJS/TEN listing colistin as a primary suspect drug. Future studies assessing this association will need to utilize large data sources with highly accurate exposure data which allows for either the exclusion or adjustment of concomitant medications which may also increase the risk of SJS/TEN. Should the association be substantiated, provider

212 education and proper adverse reaction monitoring will be key for early detection to minimize the long-term effects
213 of these serious skin reactions.
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