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Original Article

Correlation between drug–drug interaction-induced Stevens–Johnson syndrome and related deaths in Taiwan

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ABSTRACT

Concomitant use of some drugs can lead to interactions between them resulting in severe adverse effects. To date, there are few reports of incidences of Stevens-Johnson syndrome (SJS) associated with combination drug administration. Therefore, we studied the relationship between drug combinations and SJS-related mortality, with the hope that a retrospective study of this nature would provide information crucial for the prevention of future drug-drug interaction related deaths attributable to SJS. This retrospective longitudinal study used mortality cases from 1999 to 2008 that were diagnosed as erythema multiforme (International Classification of Diseases, Ninth Revision, Clinical Modification 695.1) from the National Health Insurance database in Taiwan. Statistical comparisons of the results were performed using analysis of variance (ANOVA), independent sample t-tests, and odds ratio (OR). In this way, the relationship between combinations of SJS-inducing drugs and mortality could be determined. A total of 111 patients who had died, including 63 males and 48 females (66.0 ± 20 and 70.0 ± 17.7 years, respectively), were suspected of having experienced drug-drug interaction-related adverse effects. The associated drug combinations included allopurinol and ampicillin ($p = 0.049$), carbamazepine and sulfamethoxazole/trimethoprim (TMP) ($p < 0.0001$), carbamazepine and phenytoin ($p < 0.0001$), sulfamethoxazole/TMP and phenytoin ($p = 0.015$), sulfadoxine and piroxicam ($p = 0.045$), phenobarbital and cephalexin ($p < 0.0001$), ampicillin and erythromycin ($p < 0.0001$), erythromycin and minocycline ($p < 0.0001$), and vancomycin and ethambutol ($p < 0.0001$) administered 1 month before the patients' deaths. Caution should be exercised when administering any drugs that may possibly induce SJS. In addition, attention should be paid to ensure prompt identification of possible drug-drug interactions, and patients should be closely monitored. Furthermore, medications should be immediately discontinued at the first sign or symptom suggesting the occurrence of drug-related SJS, and then prompt, adequate supportive care should be provided.

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1. Introduction

The skin is the most frequent target of adverse drug reactions, probably because it is the largest organ in the body, which also enables easy detection of these reactions when they occur. Most adverse skin reactions are related to drug hypersensitivity. Therefore, drug-related adverse cutaneous reactions are frequent, affecting 2–3% of all hospitalized patients [1]. Fortunately, only approximately 2% of adverse cutaneous reactions are severe and very few are fatal. According to statistical data from the Institute for Taiwan Drug Relief Foundation [2], a total of 1218 cases reported from 1999 to 2009 could be attributed to adverse drug events, resulting in a cost of N.T. 180 million dollars.

Skin lesions were the primary adverse effect in 337 cases (67%) while Steven–Johnson syndrome (SJS) was observed in 233 cases (46%). SJS is a systemic immune reaction of erythema multiforme. Epidemiologically, the incidence rate of SJS is 1–6 persons per year per million [3,4]. SJS could be attributed to a number of things including drugs, infections, malignant cancers, idiosyncratic characteristics, and food; however, the most common etiology is drug-induced adverse reactions (>50%) [5]. The high-risk factors for SJS include advanced age, frequent readmissions, immune dysfunction diseases, and a combination of several drugs [6–8].

Patients with SJS or toxic epidermal necrolysis tend to show relatively lower N-acetylating capacity, especially in the Caucasian population [9]. Aromatic ring-containing anticonvulsant drugs such as phenytoin, carbamazepine, and phenobarbital frequently exhibit cross-hypersensitivity [10,11], as do some other drug classes such as oxicams including the nonsteroidal anti-inflammatory drugs (NSAIDs) piroxicam and tenoxicam. Therefore, care should be exercised when choosing drugs known to be high-risk SJS-inducing agents.

2. Patients and methods

2.1. Data resource

Taiwan's National Health Insurance Research Database (NHIRD), one of the largest administrative health care databases around the world, has been used widely in academic studies. The NHIRD studies expanded rapidly in both quantity and quality since the first study was published in 2000. Researchers usually collaborated to share knowledge, which was crucial to process the NHIRD data [22]. The NHIRD includes patients' demographics, disease diagnosis, contracted medical care institutions, medical expenditure, and prescription claims data. For each medical expenditure reimbursement (both outpatient and inpatient), the types of medical services, details of medical orders, and costs are recorded. All the individual identification and medical care providers (medical professionals and institutions) were removed by the Bureau of National Health Insurance before the data were transferred to the NHRI. All the related research protocols are pre-approved by the NHRI, and investigators are required to sign an agreement that guarantees patient confidentiality before conducting any study using the NHIRD data set.

2.2. Definitions of variables

The index date was defined as the date when the first skin reaction with a diagnosis of International Classification of Diseases, Ninth Revision, Clinical Modification 695.1 (ICD-9-CM code 695.1), which represents SJS, was observed in the medical records for each of the cases. The age variable was defined as the patients' age at the time of the index date. In our study, we rechecked SJS treated with medicine such as high-dose cortisone to improve SJS diagnosis correction rate.

2.3. Study designs

The study was approved by the Institutional Review Board of the Antai Tian-Sheng Memorial Hospital. A total of 111 SJS cases (ICD-9-CME-code: 695.1) were selected from the 1999–2008 Mortality Statistics File after rejecting records that included nonspecified sex and domicile information. We used a case-controlled, longitudinal, and retrospective study design, and the data from the NHIRD between 1999 and 2008 that were included in our analysis were required to meet the following criteria. Firstly, the data was limited to that of inpatients that were diagnosed with SJS and died during that period. The definition of death cases was patients whose first admission was SJS-related and then who subsequently died at that time. That is, recovery cases were not included in our study. Secondly, the included cases had specific start times for the adverse drug reactions such as SJS, following drug administration.

Therefore, the records were screened for the administration of high-risk drugs like sulfa antibiotics [sulfamethoxazole/trimethoprim (Baktar), sulfadoxine, and sulfasalazine], oxicam derivatives (piroxicam and tenoxicam), anticonvulsants (carbamazepine, phenytoin, phenobarbital, and valproate), an antigout medication (allopurinol), penicillins (amoxicillin and ampicillin), a cephalosporin (cephalexin), a macrolide (erythromycin), a fluoroquinolone (ciprofloxacin), a glycopeptide (vancomycin), tetracyclines (doxycycline and minocycline), and antitubercular medications (rifampin and ethambutol). All records of the use of these drugs were reviewed for 1 year from the beginning of the adverse drug