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 oximams 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-CM 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 in-patients 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 sulfamethoxazole/trimethoprim (Baktar), sulfadoxine, and sulfasalazine, oxicam derivatives (piroxicam and tenoxicam), anticonvulsants (carbamazepine, phenytoin, phenobarbital, and valproate), an antibiotic medication (allopurinol), penicillins (amoxicillin and ampicillin), a cephalosporin (cefaclor), 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
reactions. As for drug–drug interactions, overlapping combined use over 3 days could be considered as an interaction.

Finally, all the study variables including the drugs, frequency, and duration of drug administration, and the different branches such as the Taipei, North, Central, Southern, Pingtung, and East branches were considered. The difference between the data sets was analyzed on a year-to-year basis.

2.4. Statistical analysis

All patients were assessed based on the SJS mortality rate. The Chi-square tests and analysis of variance were used to compare the SJS fatality prevalence between individuals with drug–drug interaction-induced SJS/toxic epidermal necrolysis and the controls. Univariate analysis and multivariate stepwise logistic regression analyses were used to identify the risk factors for mortality, and compare the prognosis of patients who received different drug therapies. The association between highly suspected drugs and risk of SJS fatality cases was estimated using the odds ratio (OR) and the 95% confidence interval (95% CI), which were calculated with unconditional logistic regression with an adjustment for age and sex. All analyses were performed using the statistical package for the social sciences (SPSS Inc., Chicago, IL, USA) version 17.0. All statistical tests were two-sided.

3. Results

As shown in Table 1, a total of 111 cases of death including 63 men and 48 women (66.0 ± 20.0 years and 70.0 ± 17.7 years, respectively), resulting from SJS were identified by screening the Taiwan National Health Insurance databank records from 1999 to 2008. The highest and lowest number of mortality cases was 53 and three from the Taipei and Eastern divisions, respectively. Specifically, the mortality prevalence rates were higher in 2007 and 2008 than they were during other years. Most patients were emergently admitted, with hospital stays lasting for 14–15 days on average before their deaths. The drug cost per patients who died increased in 2000 resulting in an increase in total drug costs. Furthermore, over 20% of patients experienced drug–drug interactions before their last admission, including those who were administered allopurinol at least 3 months prior (Table 2; p = 0.025). Of these fatalities, the most highly suspected SJS-inducing drugs such as Baktar, piroxicam, tenoxicam, phenobarbital, cephalexin, vancomycin, doxycycline, and minocycline showed an incidence rate of drug–drug combinations that was considerably lower than 10%. Therefore, drug–drug interactions were less likely to lead to SJS-induced mortality. In contrast, SJS appeared to occur following a single use of some agents including carbamazepine, Baktar, sulfadoxine, phenytoin, and ampicillin with five, seven, three, three, and three cases, respectively (31.2%, 43.7%, 18.7%, 18.7%, and 18.7%, respectively, p = 0.000). Surprisingly, regarding drug–drug interactions, we found that combinations including allopurinol and ampicillin (p = 0.049), carbamazepine and Baktar (p < 0.000), carbamazepine and phenytoin (p < 0.000), Baktar and phenytoin (p = 0.015), sulfadoxine and piroxicam (p = 0.045), phenobarbital and cephalexin (p < 0.000), ampicillin and erythromycin (p < 0.000), erythromycin and minocycline (p < 0.000) versus vancomycin and ethambutol (p < 0.000) were administered 1 month before the deaths of these patients (Table 3).

The individual end points of the sex- and age-adjusted univariate and multivariate analyses revealed that patients who were administered cephalexin had the highest risk of death resulting from SJS complications (Table 4; OR 13.429, 95% CI 1.141–158.006, p = 0.009). In addition, minocycline (OR 13.429, 95% CI 1.141–158.006, p = 0.009), followed by Baktar (OR 11.537, 95% CI 3.182–41.829, p = 0.000) and allopurinol (OR 3.318, 95% CI 1.116–9.867, p = 0.025) had significantly high incidences of SJS-induced mortality.

For comparison of the differences in the area under the curve (AUC), a receiver operating characteristic curve was used. Based on the receiver operating characteristic curve, allopurinol was the best option for reducing SJS-induced deaths with the highest accuracy; the sensitivity and specificity were 88.3% and 80.9%, respectively, with an AUC of 0.88 (Fig. 1). The AUC values for other drugs were 0.77%, 0.74%, and 0.60% for cephalexin, minocycline, and Baktar, respectively, (Fig. 1). The AUC values for other drugs were 0.77%, 0.74%, and 0.60% for cephalexin, minocycline, and Baktar, respectively, with an AUC of 0.88 (Fig. 1). The AUC values for other drugs were 0.77%, 0.74%, and 0.60% for cephalexin, minocycline, and Baktar, respectively, with an AUC of 0.88 (Fig. 1). The AUC values for other drugs were 0.77%, 0.74%, and 0.60% for cephalexin, minocycline, and Baktar, respectively, with an AUC of 0.88 (Fig. 1).

### Table 1 – Baseline characteristics of 111 Stevens–Johnson syndrome-induced mortality cases from 1999 to 2008 in the National Health Insurance databank.

| Yr | Cases (yr; mean ± SD) | D of acute admission (mean ± SD) | D of chronic admission (mean ± SD) | Total annual cost (N.T. dollars/person) | Total annual drug cost (N.T. dollars/person) |
|----|----------------------|---------------------------------|-----------------------------------|---------------------------------------|------------------------------------------|
| 1999 | 8 | 67.0 ± 28.8 | 14.4 ± 7.5 | 0 ± 0 | 164,901,000 | 35,645,250 |
| 2000 | 6 | 57.2 ± 27.9 | 23.1 ± 26.1 | 0 ± 0 | 522,811,667 | 155,461,555 |
| 2001 | 8 | 62.5 ± 24.6 | 8.4 ± 9.4 | 0 ± 0 | 111,582,250 | 24,568,875 |
| 2002 | 8 | 56.3 ± 28.5 | 13.7 ± 12.0 | 0 ± 0 | 209,861,615 | 65,318,230 |
| 2003 | 6 | 66.2 ± 24.1 | 19.0 ± 6.3 | 0 ± 0 | 351,826,167 | 97,085,667 |
| 2004 | 12 | 65.4 ± 21.7 | 14.3 ± 11.5 | 0 ± 0 | 264,409,076 | 78,058,153 |
| 2005 | 12 | 68.7 ± 14.3 | 15.2 ± 16.2 | 0.4 ± 1 | 194,497,574 | 47,730,357 |
| 2006 | 5 | 75.4 ± 8.8 | 15.8 ± 13.1 | 0 ± 0 | 214,781,778 | 51,899,222 |
| 2007 | 20 | 70.3 ± 13.5 | 15.5 ± 14.0 | 1 ± 4.4 | 156,656,074 | 39,664,571 |
| 2008 | 26 | 75.0 ± 14.6 | 14.4 ± 12.8 | 0 ± 0 | 167,165,029 | 33,776,9706 |
| Total | 111 | 68.2 ± 19.7 | 14.8 ± 13.8 | 0.2 ± 2.0 | 205,599,134 | 52,932,2685 |

SD = standard deviation.
4. Discussion

Our study is the first population-based, nested case-control study using a data set of 111 SJS-induced fatality patients...
with their complete prescriptions and diagnoses over a 10-year period. Based on this extensive data sample, we were able to include enough patients from the same population with incidences of SJS to examine the exposure to high-risk drugs, especially allopurinol and cephalexin. We found that with modified effects from age or sex, allopurinol, cephalexin, minocycline, and Baktar were associated with higher risks of SJS in patients than the other drugs were. The relationship between allopurinol and SJS is more established [12] than that of the other drugs. Moreover, our finding provides evidence to support a relationship between the single-use of allopurinol and SJS. The issue of drug interaction has emerged as a cause of increasing concern because of the increased likelihood of combined drug treatment for numerous patients. We analyzed the risks of the multiple combinations including allopurinol and ampicillin, carbamazepine and Baktar, carbamazepine and phenytoin, Baktar and phenytoin, sulfadoxine and piroxicam, phenobarbital and cephalexin, ampicillin and erythromycin, erythromycin and minocycline, and vancomycin and ethambutol. As for combined exposure and then increasing SJS incidence rate in a study by Lawrence and Dahl [21], seven patients were treated with low dose of methotrexate and NSAIDs for psoriatic plaque and pre-existing dermatitis. However, the fact that fewer patients were exposed to these combinations in our study might explain the contrast between our results and those of a recent study in Taiwan. The results of that study, which involved the analysis of increased risk of skin reactions following the administration of a combination of the two mood stabilizers, implied that lamotrigine, similar to carbamazepine and valproate may cause SJS. In addition, co-administration with valproate may further increase the risk [13,14]. Surprisingly, we did not find an increased risk of SJS for the use of carbamazepine, which is the drug most known to induce SJS [4,15–19].

Table 4 – Univariate and multivariate methods (sex- and age-adjusted).

| Items        | Odds ratioa | 95% CIa | p (univariate) | p (multi-variate) |
|--------------|-------------|---------|----------------|-------------------|
| Sex          | 1.375       | 0.476–3.974 | 0.047          | 0.560             |
| Age          | 1.130       | 0.334–3.822 | 0.570          | 0.845             |
| Allopurinol  | 3.318       | 1.116–9.867 | 0.013*         | 0.025*            |
| Carbamazepine| 0.104       | 0.059–0.182 | 0.493          | 0.0001*           |
| Baktar       | 11.537      | 3.182–41.829 | 0.0001*        | 0.0001*           |
| Sulfadoxine  | 0.120       | 0.072–0.200  | 0.605          | 0.683             |
| Piroxicam    | 0.855       | 0.791–0.923  | 0.805          | 0.873             |
| Tenoxicam    | 0.855       | 0.791–0.923  | 0.805          | 0.873             |
| Phenytoin    | 0.120       | 0.072–0.200  | 0.047          | 0.0001*           |
| Phenobarbital| 6.267       | 3.72–105.648 | 0.549          | 0.151             |
| Ampicillin   | 1.200       | 0.131–10.999 | 0.606          | 0.873             |
| Cephalexin   | 13.429      | 1.141–158.006 | 0.0001*        | 0.009*            |
| Erythromycin | 0.136       | 0.085–0.218  | 0.060          | 0.014*            |
| Vancomycin   | 4.381       | 0.672–28.581 | 0.881          | 0.097             |
| Doxycycline  | 6.267       | 0.372–105.648 | 0.003*         | 0.151             |
| Minocycline  | 13.429      | 1.141–158.006 | 0.303          | 0.009*            |
| Ethambutol   | 0.136       | 0.085–0.218  | 0.0001*        | 0.014*            |

*p < 0.05 was significant.

All data were tested using unconditional logistic regression; CI = confidence interval.

Fig. 1 – Receiver operating characteristics curve for diagnosis of high-risk Stevens–Johnson syndrome-inducing drugs. Receiver operating characteristics of allopurinol, cephalexin, minocycline, and Baktar are shown. Allopurinol has a sensitivity of 0.883 and specificity of 0.809 and, therefore, could be considered to exhibit most risk for inducing SJS. AUC = area under the curve; ROC = receiver operating characteristics.
5. Conclusion

Based on the results of our analysis, we strongly recommend that caution should be exercised in the use of any drugs that may possibly induce SJS. In addition, patients administered these suspected drugs should be observed and monitored for possible drug–drug interactions. Furthermore, the suspected medications should immediately be discontinued at the first signs of SJS, and supportive care should be provided promptly. In particular, patients who have experienced SJS should avoid future contact with the implicated drugs.

Conflicts of interest

The authors have nothing to disclose.

REFERENCES

[1] Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. Pharmacol Rev 2001;53:357–79.
[2] Taiwan Drug Relief Foundation TDRF. Available at: http://www.tdrf.org.tw/. [date accessed 14.06.15].
[3] Schöpf E, Stühmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. Toxic epidermal necrolysis and Stevens–Johnson syndrome. An epidemiologic study from West Germany. Arch Dermatol 1991;127:839–42.
[4] Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, Walker AM. The incidence of erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol 1990;126:43–7.
[5] Letko E, Papaliodis DN, Papaliodis GN, Daoud YJ, Ahmed AR, Foster CS. Stevens–Johnson syndrome and toxic epidermal necrolysis: a review of the literature. Ann Allergy Asthma Immunol 2005;94:119–36.
[6] Kumar A, Edward N, White MI, Johnston PW, Catto GR. Allopurinol, erythema multiforme, and renal insufficiency. BMJ 1996;312:173–4.
[7] Jick H, Porter JB. Potentiation of ampicillin skin reactions by allopurinol or hyperuricemia. J Clin Pharmacol 1981;21:456–8.
[8] Rådevand E, Sletvold O, Kvande KT. Side effects off allopurinol. Tidsskr Nor Laegeforen 2004;124:2618–9.
[9] Dietrich A, Kawakubo Y, Rzany B, Mockenhaupt M, Simon JC, Schöpf E. Low N-acetylator capacity in patients with Stevens–Johnson syndrome and toxic epidermal necrolysis. Exp Dermatol 1995;4:313–6.
[10] Sullivan JR, Shear NH. The drug hypersensitivity syndrome: what is the pathogenesis? Arch Dermatol 2001;137:357–64.
[11] Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. Neurology 1997;49:542–6.
[12] Rzany B, Correia O, Kelly JP, Naldi I, Auquier A, Stern R. Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. Lancet 1999;353:2190–4.
[13] Mockenhaupt M, Viboud C, Dunant D, Naldi I, Haley S, Bouwes Bavinck JN, Sidoroff A, Schneck J, Roujeau JC, Flahault A. Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol 2008;128:35–44.
[14] Huang CW, Tsai JJ, Lai ML. Lamotrigine-related skin rashes in adults. Kaohsiung J Med Sci 2002;18:566–72.
[15] Bigny M, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston collaborative drug surveillance program on 15,438 consecutive inpatients, 1975 to 1982. JAMA 1986;24:3358–63.
[16] Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272–85.
[17] Farthing P, Bagan JV, Scully C. Mucosal disease series. Number IV. Erythema multiforme. Oral Dis 2005;11:261–7.
[18] Wolkenstein P, Revuz J. Drug-induced severe skin reactions. Incidence, management and prevention. Drug Saf 1995;13:56–68.
[19] Assier H, Bastuji-Garin S, Revuz J, Roujeau JC. Erythema multiforme with mucous membrane involvement and Stevens–Johnson syndrome are clinically different disorders with distinct causes. Arch Dermatol 1995;131:539–43.
[20] Roujeau JC, Kelly JP, Naldi I, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F, Mockenhaupt M, Paolletti C, Shapiro S, Shear N, Schöpf E, Kaufman DW. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600–7.
[21] Lawrence CM, Dahl MG. Two patterns of skin ulceration induced by methotrexate in patients with psoriasis. J Am Acad Dermatol 1984;11:1059–65.
[22] Chen Yu-Chun, Yeh Hsiao-Yun, Wu Jau-Ching, Haschler Ingo, Chen Tzeng-Ji, Wetter Thomas. Taiwan’s National Health Insurance Research Database: administrative health care database as study object in bibliometrics. Scientometrics 2011;86:365–80.