Outbreak of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Associated With Mebendazole and Metronidazole Use Among Filipino Laborers in Taiwan

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Objectives. This study sought to identify the risk factors associated with an outbreak of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) among Filipino laborers in Taiwan.

Methods. Forty-six SJS/TEN patients were matched to 92 controls according to month of arrival in Taiwan, sex, and age.

Results. The odds ratio for development of SJS/TEN was 9.5 (95% confidence interval [CI]=3.9, 23.9) among workers who had used both metronidazole and mebendazole sometime in the preceding 6 weeks. In addition, a gradient increase in the occurrence of SJS/TEN was found with an increasing level of exposure to metronidazole.

Conclusions. This outbreak highlights the risk of SJS/TEN resulting from the use of both metronidazole and mebendazole and the need for control measures. (*Am J Public Health.* 2003;93:489–492)

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are acute, life-threatening conditions. TEN and SJS are thought to be qualitatively identical disorders that differ only in the extent of body surface involved and the severity of systemic signs.[1,2] TEN is characterized by the sudden onset of epidermal necrosis and extensive skin detachment involving 30% of the body surface or more. The prognosis is poor, with a case fatality rate of 30% to 40%.[1,2] Milder forms are known as SJS or SJS/TEN overlap.

SJS is characterized by extensive small blisters with skin detachment over less than 10% of the body surface; blisters with skin detachment levels of 10% to 29% are classified as having SJS/TEN overlap.[2–5] SJS has been associated with the use of sulfadoxine and the combination of sulfadoxine and pyrimethamine.[6] Although SJS/TEN has been reported to occur secondary to use of other drugs, including thiabendazole[2] and metronidazole,[7] it has not been reported to occur after administration of both metronidazole and mebendazole.

Since October 1989, laborers from various Southeast Asian countries have been allowed to work in Taiwan. Every foreign laborer is currently required to undergo a general physical examination before entry into employment, within 7 days after entry, and then every 6 months during his or her employment. A general physical examination, which includes a stool test for intestinal parasites (e.g., amebic dysentery, protozoa), has been a requirement for employment since 1993.[8] Many laborers take anthelmintic drugs such as metronidazole, mebendazole, or pyrantel pamoate to avoid a positive stool test at the time of the 7-day examination.

In August 1996, 6 female Filipino workers at an electronics factory in Taiwan were hospitalized as a result of skin rash, fever, and elevation of liver transaminases. The outbreak was reported to the local health department. The patients' blood samples were sent to the National Institute of Preventive Medicine for serum antibody testing for Epstein-Barr virus, cytomegalovirus, measles, rubella, herpes, hepatitis A, HIV/AIDS, and *Rickettsia* spp. All of the tests were negative. One of the 6 patients died, and the other 5 recovered after hospitalization. All of the foreign laborers at this factory shared dormitory rooms.

When 4 more Filipino female workers at the same factory were later hospitalized with the same clinical outlook in November 1996, an investigation was undertaken by a team from the Field Epidemiology Training Program. This retrospective case–control study examined the determinants of the development of SJS/TEN among patients whose condition was reported to the Department of Health during the outbreak.

METHODS

Case Definition

The study included patients who were admitted to the hospital with a diagnosis of SJS/TEN between February 1996 and January 1997 and who were later classified as having SJS/TEN by 2 experienced dermatologists. The dermatologists reviewed photographs and medical records but did not have data on patients' exposure to possible etiological agents. Discrepancies in classification were adjudicated by a third dermatologist.

The classification guidelines described by Bastuji-Garin et al. were used.[5] Patients' conditions were categorized as follows: (1) SJS (characterized by widespread small blisters and skin detachment levels of less than 10% of the body surface area), (2) overlapping SJS/TEN (skin detachment levels of 10% to 29% of the body surface area), or (3) TEN (widespread detachment of epidermis involving 30% or more of the body surface area). The latent period of exposure was defined as the duration between the first day of drug intake and the day of onset of symptoms or signs (rash, blisters or definite erosion of the skin or mucous membranes).

Case Finding

On February 10, 1997, the Department of Health requested that clinicians report all patients admitted to Taiwan hospitals with a diagnosis of SJS/TEN during the period from February 1996 through January 1997. A total of 115 patients with a physician diagnosis of SJS/TEN were reported to the Department of Health. However, the reviews con-

ducted by dermatologists excluded 62 patients owing to an unmet case definition, leaving 53 for inclusion in this study.

Controls

Two controls were selected for each case patient. All controls were Filipino workers in other factory dormitory rooms, and they were matched to case patients in terms of month of arrival in Taiwan, sex, and age (within 3 years).

Questionnaire

A questionnaire was administered, by means of a personal interview, to available case patients and controls. Data collected included demographic characteristics, medical history, contraceptive methods used, sexual history, drug intake, and use of Chinese herbal remedies. Information on drug intake was gathered for the 6 weeks preceding hospitalization.[5] Controls were asked about their drug intake for the 6 weeks preceding hospitalization of their matched case patient.

A list of brand names of the drugs of interest was shown to the patients and controls to assist with identification. These drugs included sulfonamides, nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antibiotics, and anthelmintic drugs (metronidazole, mebendazole, pyrantel pamoate). In the case of each drug taken, timing, dose, indications, previous drug exposures, and previous adverse reactions were recorded.

Laboratory and Microbiological Examination

Blood samples obtained from the 53 patients were subjected to testing that included blood count, chemistries, routine bacterial cultures, antibody for Epstein-Barr virus, cytomegalovirus, measles, rubella, herpes, hepatitis A, HIV/AIDS, and *Rickettsia* spp. All tests were conducted at the laboratory of the National Institute of Preventive Medicine.

Statistical Analysis

Associations between illness and various risk factors were assessed for statistical significance via χ^2 tests and Yates corrections. A 2-sided P value below .05 was considered statistically significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated.

RESULTS

The 53 cases of SJS/TEN included in the study comprised 2 males (3.8%) and 51 females (96.2%). The disease was further classified as TEN in 5 (10%) patients, overlap SJS/TEN in 3 (6%) patients, and SJS in 45 (84%) patients. All of these cases occurred among Filipino workers employed in 7 factories that manufactured electronics, textiles, automobiles, and other goods. During the study period, a total of 1684 Filipino workers (12% male, 88% female) began employment in these 7 factories.

The overall attack rate was 3.1% (53 of 1684). The attack rate was not statistically different among the factories (varying from 0.7% to 4.8%; $P>.05$) or among male (3.4%) and female (1.0%) workers ($P>.05$). The variations in attack rate in the different factories might have been due to the small number (<250) of Filipino workers employed in 6 of these factories. Among these case patients, 5 with TEN died of sepsis. No cases of SJS/TEN occurred in these laborers' 12 000 Taiwanese coworkers during the study period.

The first of the 53 case patients was hospitalized in February 1996, and the last was hospitalized in January 1997. The peak rate of illness occurred in November 1996, which coincided with the timing of medical examinations of the foreign workers. The most common signs and symptoms self-reported by patients included fever (100%), erosion or blisters of mucous membranes (100%), rash (92%), muscle pain (62%), jaundice (53%), vomiting (46%), and skin detachment (31%); hypotension (15%) and diarrhea (8%) were rather uncommon. Laboratory investigations revealed high levels of liver transaminases (more than 2 times the normal range; 66%), leukocytosis (≥10 000/mm^3; 34%), and leukopenia (≥4000/mm^3; 21%).

Case–Control Study

Of the 53 case patients, 5 died; 2 of the male patients had returned to the Philippines by the time of investigation and hence were excluded from this study. Forty-six triads were included in the analysis, representing 46 case patients and 92 controls. The case patients and controls were similar with regard to all characteristics examined except for use of anthelmintic agents.

TABLE 1—Characteristics of Case–Control Study Population and Evaluation of Potential Risk Factors for Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

Characteristic	Case Patients (n = 46)	Controls (n = 92)
Female, No. (%)	46 (100)	92 (100)
Age, y, mean (SD)	24 (0.7)	25 (1.2)
Single, No. (%)	41 (89)	83 (90)
Contraception use, No. (%)	0 (0)	0 (0)
Product used at menstruation, No. (%)		
Tampon	0 (0)	0 (0)
Napkin	46 (100)	92 (100)
Medication use, No. (%)		
Sulfonamide antimicrobials	0 (0)	0 (0)
Ampicillin	1 (2)	0 (0)
Anticonvulsants	0 (0)	0 (0)
NSAIDs	0 (0)	0 (0)
Mebendazole*	41 (89)	42 (46)
Metronidazole*	40 (87)	29 (32)
Pyrantel pamoate*	0 (0)	44 (48)

Note. Continuous variables were assessed via *t* tests; categorical variables were assessed via χ^2 tests. Significance levels refer to associations with risk for SJS/TEN. NSAIDs = nonsteroidal anti-inflammatory drugs.
*$P<.001$.

In the univariate analysis, risk of SJS/TEN was associated with mebendazole use and metronidazole use (each $P<.001$) (Table 1). No significant differences were found between case patients and controls in terms of sex; mean age; marital status; sexual activity in the absence of birth control; use of deodorized tampons or sanitary napkins; use of sulfonamides, antibiotics, anticonvulsants, or NSAIDs; and type of work.

Relationships between mebendazole and metronidazole use and risk of SJS/TEN are summarized in Table 2. The risk of SJS/TEN was significantly higher among individuals who had used both mebendazole and metronidazole sometime in the previous 6 weeks

TABLE 2—Risk of Occurrence of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, by Anthelmintic Drug Use

	Case Patients (n = 46), No.	Controls (n = 92), No.	Odds Ratio (95% Confidence Interval)
Pyrantel pamoate only			. . .
Yes	0	44	
No	46	48	
Mebendazole only			0.5 (0.1, 1.6)
Yes	6	19	
No	40	73	
Metronidazole only			1.8 (0.3, 8.6)
Yes	5	6	
No	41	86	
Mebendazole + metronidazole			9.5 (3.9, 23.9)*
Yes	35	23	
No	11	69	

*$P < .001$ (χ^2 test).

TABLE 3—Risk of Occurrence of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, by Exposure Dosages of Metronidazole and Mebendazole

	Case Patients, No.	Controls, No.	Odds Ratio[a] (95% Confidence Interval)
Dosage of metronidazole, mg[b]			
500–1000	4	14	1.0 (referent)
1500	4	4	3.5 (0.4, 30.9)
≥ 2000	27	5	18.9 (3.6, 112.8)**
Dosage of mebendazole, mg[c]			
500–1000	28	11	1.0 (referent)
1500	3	1	1.2 (0.1, 32.9)
≥ 2000	4	11	0.1 (0.03, 0.6)*

[a] χ^2 test.
[b] χ^2 for trend = 18.7, $P < .0001$.
[c] χ^2 for trend = 8.4, $P < .05$.
*$P < .05$; **$P < .001$.

(OR = 9.5; 95% CI = 3.9, 23.9; $P < .001$) but was not significantly higher among those who had used only pyrantel pamoate, only mebendazole, or only metronidazole.

Table 3 shows the dose–response relationship between SJS/TEN and exposure level to metronidazole among combined mebendazole and metronidazole users. It can be seen that there was an increasing trend in SJS/TEN risk with increasing level of exposure to metronidazole. A reverse dose–response relationship was found between risk of SJS/TEN and level of exposure to mebendazole.

The median latent period of exposure was 22 days (range: 11–32 days). About 50% of the cases occurred within 22 to 28 days after patients had taken metronidazole or mebendazole.

Microbiological Examination

Blood samples obtained from 46 case patients were all negative for routine bacterial cultures and IgM antibody for Epstein-Barr virus, cytomegalovirus, measles, rubella, herpes simplex, hepatitis A, *Rickettsia* spp, and HIV antibody.

DISCUSSION

A drug etiology for SJS/TEN is easy to postulate but difficult to prove. Because no reliable skin or laboratory tests are available, skillful collection of patient histories remains the best tool for identifying a particular drug as the trigger of SJS/TEN. Although rechallenge tests would provide convincing evidence, such testing is not feasible for ethical reasons.

Because use of mebendazole and metronidazole has been suspected as the cause of SJS/TEN in Taiwan, several measures have been implemented to prevent further cases. Unnecessary prescription of anthelmintic drugs during predeparture medical screening of overseas Filipino workers has been discontinued; only those workers who have tested positive for parasites are now treated, and it is recommended that mebendazole and metronidazole not be used in combination. Any Filipino workers with suspected symptoms of TEN/SJS are hospitalized immediately. This intervention appears to have been effective, as shown by an absence of new cases observed during the following 2-year period.

In this outbreak, a striking difference in attack rates was observed between workers who were prescribed the 2 anthelmintic drugs by doctors in the Philippines and those who were not, suggesting a causative role of these drugs in the initiation of SJS/TEN. The implication of a causative role of anthelmintic drugs in this outbreak was further supported by the finding that all patients had recently arrived in Taiwan. No additional cases occurred after practices were changed in the Philippines to stop the routine prescription of anthelmintic drugs to workers going abroad. That no cases were observed among local Taiwanese workers—and no secondary cases were found among factory workers—strongly implies that the outbreak was not due to a microorganism. Furthermore, although the Filipino workers made up only a small proportion of the total workforce, they included all cases of SJS/TEN observed during this period.

Several cases of SJS/TEN associated with use of thiabendazole[2,9] or metronidazole[7] have been reported. Mebendazole and metronidazole are generally safe if 1 of the agents is used in a low dosage. In our series, all of the patients had taken high doses

(>500 mg) of either metronidazole or mebendazole. Our results indicated that the risk of SJS/TEN increased with increasing doses of metronidazole (Table 3). In contrast, a reverse dose–response relationship was found with mebendazole, which might have been due to combined use with a lower dose of metronidazole. This could explain why a drug that is normally safe might produce these severe reactions.[10]

Another possible cause of the outbreak is a synergistic interaction between mebendazole and metronidazole. Our results showed that whereas the risk of SJS/TEN was not significantly higher among individuals who used only pyrantel pamoate, only mebendazole, or only metronidazole, it was remarkably higher among those who used both mebendazole and metronidazole (OR=9.5; 95% CI=3.9, 23.9; $P<.001$) (Table 2).

As mentioned earlier, SJS/TEN is an acute, life-threatening condition. Epidermal necrosis causes erosion of mucous membranes, extensive detachment of the epidermis, and severe extracutaneous symptoms (fever, prostration, internal organ involvement).[11] The physiopathological mechanisms underlying these conditions have not been established. When skin detachment is extensive, however, the prognosis is poor.

Drugs are an important cause of SJS/TEN.[12] Drug-induced SJS/TEN typically occurs 1 to 3 weeks after initiation of therapy, and it may occur more quickly with readministration of drugs.[13] Other reports of SJS and occasional reports of TEN have been associated with chemical exposure, mycoplasma infection, viral infections, and immunization.[14,15] In addition, genetic susceptibility or environmental factors may play a role.[16] In our study, the concentrations of chemicals (e.g., lead, organic solvents) inside the factories were within normal limits (data not shown). Also, we did not find any infection markers among case patients taking part in this study.

Our findings are based on self-report data, and thus responses may have been subject to a certain degree of recall bias. However, there is no reason to believe that this potential bias had any impact on the statistical results. As mentioned, the drugs were shown to the patients and controls to assist with identification. Moreover, a multitrait–multimethod analysis of independent ratings has concluded that self-report data is valid.[17]

We conclude that combination therapy involving metronidazole and mebendazole should be avoided, because of the increased risk of SJS/TEN. Higher doses of metronidazole were shown to increase the risk of severe cutaneous adverse reactions. The outbreak described here highlights the likelihood that if steps are not taken to increase awareness, future outbreaks may occur as a result of the use of high doses of metronidazole and mebendazole. Programs designed to increase awareness among those physicians who are more likely to prescribe the causative drugs and to educate workers about the risks of developing this condition may prevent further disease occurrence. ■

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Contributors

K.T. Chen planned the study, analyzed the data, and wrote the article. S.J. Twu designed the questionnaire and assisted with the data analysis. H.J Chang assisted with the data analysis. R.S. Lin supervised the data analysis and contributed to the writing of the article.

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Human Participant Protection

This study was approved by the institutional review board of the Taiwan Center for Disease Control.

References

1. Chean HL, Stern RS, Arndt KA, et al. 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;126:43–47.

2. Fritsch PO, Ruiz-Maldonado R. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In: *Fitzpatrick's Dermatology in General Medicine.* 5th ed. New York, NY: McGraw-Hill Book Co; 1999:636–654.

3. Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin. *Br J Dermatol.* 1956; 68:355–361.

4. Tyson R, Walker J. An unusual bullous eruption. *S Afr Med J.* 1956;30:97–98.

5. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol.* 1993;129: 92–96.

6. Hernborg A. Stevens-Johnson syndrome after mass prophylaxis with sulfadoxine for cholera in Mozambique. *Lancet.* 1985;2(8463):1072–1073.

7. Egan CA, Grant WJ, Morris SE, Saffle JR, Zone JJ. Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis. *J Am Acad Dermatol.* 1999;40: 458–461.

8. *Public Health in Taiwan.* Taiwan, Republic of China: Taiwan Dept of Health; 1998.

9. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* 1995;333: 1600–1607.

10. Chan HL. Observation on drug-induced toxic epidermal necrolysis in Singapore. *J Am Acad Dermatol.* 1984;10:973–978.

11. Snyder RA, Elias PM. Toxic epidermal necrolysis and staphylococcal scalded skin syndrome. *Dermatol Clin.* 1983;1:235–238.

12. Yetiv JZ, Bianchine JR, Owen JA Jr. Etiologic factors of the Stevens-Johnson syndrome. *South Med J.* 1980;73:599–602.

13. Roujeau JC, Stern RS. Severe adverse cutaneous reaction to drugs. *N Engl J Med.* 1994;331: 1272–1285.

14. House RA, Jakubovic H, Wong L, Holness DL. Work-related toxic epidermal necrolysis? *J Occup Med.* 1992;34:135–139.

15. Nethercott JR, Choi BC. Erythema multiforme (Stevens-Johnson syndrome)—chart review of 123 hospitalized patients. *Dermatologia.* 1985;171:383–396.

16. Roujeau JC, Huynh TN, Bracq C, Guillaume JC, Revuz J, Touraine R. Genetic susceptibility to toxic epidermal necrolysis. *Arch Dermatol.* 1987;123: 1171–1173.

17. Stacy AW, Widaman KF, Hays R, DiMatteo MR. Validity of self-reports of alcohol and other drug use: a multitrait-multimethod assessment. *J Pers Soc Psychol.* 1985;49:219–232.