MEDICATION USE AND THE RISK OF STEVENS–JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS

JEAN-CLAUDE ROUJEAU, M.D., JUDITH P. KELLY, M.S., LUIGI NALDI, M.D., BERTHOLD RZANY, M.D., ROBERT S. STERN, M.D., THERESA ANDERSON, R.N., ARIANE AUQUIER, M.S., SYLVIE BASTUJI-GARIN, M.D., OSVALDO CORREIA, M.D., FRANCESCO LOCATI, M.D., MAJA MOCKENHAUPT, M.D., CATHERINE PAOLETTI, SAMUEL SHAPIRO, M.B., F.R.C.P.(E.), NEIL SHEAR, M.D., ERWIN SCHÖPF, M.D., AND DAVID W. KAUFMAN, SC.D.

Abstract *Background.* Toxic epidermal necrolysis and Stevens–Johnson syndrome are rare, life-threatening, drug-induced cutaneous reactions. We conducted a case–control study to quantify the risks associated with the use of specific drugs.

Methods. Data were obtained through surveillance networks in France, Germany, Italy, and Portugal. Drug use before the onset of disease was compared in 245 people who were hospitalized because of toxic epidermal necrolysis or Stevens–Johnson syndrome and 1147 patients hospitalized for other reasons (controls). Crude relative risks were calculated and adjusted for confounding by multivariate methods when numbers were large enough.

Results. Among drugs usually used for short periods, the risks were increased for trimethoprim–sulfamethoxazole and other sulfonamide antibiotics (crude relative risk, 172; 95 percent confidence interval, 75 to 396), chlormezanone (crude relative risk, 62; 21 to 188), aminopenicillins (multivariate relative risk, 6.7; 2.5 to 18), quinolones (multivariate relative risk, 10; 2.6 to 38), and cephalosporins (multivariate relative risk, 14; 3.2 to 59). For acetaminophen, the multivariate relative risk was 0.6 (95 percent confidence interval, 0.2 to 1.3) in France but 9.3 (3.9 to 22) in the other countries. Among drugs usually used for months or years, the increased risk was confined largely to the first two months of treatment, when crude relative risks were as follows: carbamazepine, 90 (95 percent confidence interval, 19 to ∞); phenobarbital, 45 (19 to 108); phenytoin, 53 (11 to ∞); valproic acid, 25 (4.3 to ∞); oxicam nonsteroidal antiinflammatory drugs (NSAIDs), 72 (25 to 209); allopurinol, 52 (16 to 167); and corticosteroids, 54 (23 to 124). For many drugs, including thiazide diuretics and oral hypoglycemic agents, there was no significant increase in risk.

Conclusions. The use of antibacterial sulfonamides, anticonvulsant agents, oxicam NSAIDs, allopurinol, chlormezanone, and corticosteroids is associated with large increases in the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. But for none of the drugs does the excess risk exceed five cases per million users per week. (N Engl J Med 1995;333:1600-7.)

TOXIC epidermal necrolysis and Stevens–Johnson syndrome are acute life-threatening conditions. Epidermal necrosis causes erosions of the mucous membranes, extensive detachment of the epidermis, and severe constitutional symptoms.[1,2] The physiopathologic mechanisms of these conditions are not established. When there is very extensive skin detachment (Fig. 1) and a poor prognosis (death rates of 30 to 40 percent), the condition is usually called toxic epidermal necrolysis. Milder forms are known as Stevens–Johnson syndrome (Fig. 2) or overlapping Stevens–Johnson syndrome and toxic epidermal necrolysis.[3] Toxic epidermal necrolysis is usually drug-related.[1,2] Drugs are an important cause of Stevens–Johnson syndrome, but infections or a combination of infections and drugs has also been implicated.[4] In case reports and studies, more than 100 drugs have been implicated as causes of Stevens–Johnson syndrome or toxic epidermal necrolysis.[1,2,5-10] A limited number of drugs, including sulfonamides, anticonvulsant agents, and allopurinol, are the most consistently associated with the conditions; whether nonsteroidal antiinflammatory drugs (NSAIDs), analgesic agents, and nonsulfonamide antibiotics are associated with them is controversial. The relative risk associated with the use of specific drugs has never been quantified.

The incidence of toxic epidermal necrolysis is estimated at 0.4 to 1.2 cases per million person-years[8,9,11,12] and of Stevens–Johnson syndrome, at 1 to 6 cases per million person-years.[9,11] Although infrequent, these conditions may kill or severely disable previously healthy people. A few cases have prompted the withdrawal of newly released drugs.[2] The medical and economic impact of these disorders is therefore greater than might be expected on the basis of incidence. Better information on these reactions should help in medical decision making. We conducted a large international case–con-

From the Groupe Epidemiologie LY Stevens–Johnson (ELYS), Department of Dermatology (J.-C.R.), and the Department of Public Health (S.B.-G.), Université Paris XII, Créteil, France; the Slone Epidemiology Unit, Boston University School of Medicine, Boston (J.P.K., T.A., S.S., D.W.K.); Gruppo Italiano Studi Epidemiologici in Dermatologia, Department of Dermatology, Università degli Studi di Milano, Bergamo, Italy (L.N., F.L.); Dokumentationszentrum schwerer Hautreaktionen, Department of Dermatology, Albert-Ludwigs-Universität, Freiburg, Germany (B.R., M.M., E.S.); the Department of Dermatology, Beth Israel Hospital, Harvard Medical School, Boston (R.S.S.); the Department of Biostatistics and Epidemiology, INSERM Unité 351, Institut Gustave-Roussy, Villejuif, France (A.A., C.P.); Grupo Português ELYS, Department of Dermatology and Immunology, Hospital S. João, Faculdade de Medicina, Porto, Portugal (O.C.); and the Department of Pharmacology, Sunnybrook Health Science Centre, Toronto (N.S.). Address reprint requests to Dr. Roujeau at the Service de Dermatologie, Hôpital H. Mondor, 94010 Créteil, France.

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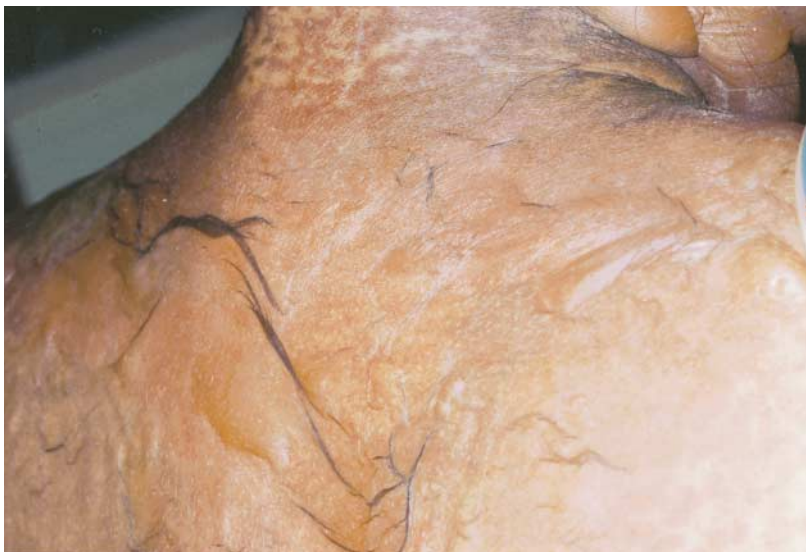

Figure 1. Typical Pattern of Toxic Epidermal Necrolysis.
Blisters and wrinkled areas result from full-thickness necrosis of the epidermis.

trol study to quantify the association of specific drugs with Stevens–Johnson syndrome and toxic epidermal necrolysis.

Methods

Case–Control Design

Because of the low expected incidence of Stevens–Johnson syndrome and toxic epidermal necrolysis, a case–control study with a very large population base was the most feasible method for quantifying the risks.[13] The study was conducted through extensive surveillance networks, covering about 120 million inhabitants of France, Germany, Italy, and Portugal. Data collection began between February 1989 (in Italy) and March 1992 (in Germany). It ended in France on January 31, 1993, and continues in the other countries. This analysis includes all subjects enrolled through June 30, 1993.

Potential case patients were identified through regular and frequent contacts with hospital departments treating such patients (e.g., burn units, intensive care units, dermatology departments, and pediatrics departments). In Germany, the case–control study was conducted as part of a registry of severe skin reactions. After obtaining informed consent, trained physicians used a structured questionnaire to interview potential case patients, along with three controls matched for sex and age to each case patient.

Case Patients

Potential case patients were those admitted to the hospital with a diagnosis of toxic epidermal necrolysis, Stevens–Johnson syndrome, or a related condition (erythema exsudativum multiforme majus, or erythema multiforme major). Cases were validated and classified by an international group of dermatologists who reviewed photographs, pathological slides, and standardized clinical information but who were not given the data on the patients' exposure to possible etiologic agents. The classification rules[3] for these conditions were applied to all potential cases.

Potential case patients were either excluded or accepted and classified as having possible, probable, or definite disease. Only patients for whom there were biopsy data, photographs, or both were classified as having definite disease. To avoid confusion with children with staphylococcal scalded skin syndromes, children were included only if they had mucous-membrane erosions or target-like lesions, or had had a skin biopsy. Patients' conditions were categorized as unclassifiable (because of a lack of information), milder forms of erythema multiforme major (characterized by mucous-membrane erosions and typical targets acrally distributed) or of either erythema multiforme major or Stevens–Johnson syndrome (if data were insufficient or ambiguous), or one of three more severe forms: Stevens–Johnson syndrome (characterized by widespread small blisters, with skin detachment of less than 10 percent of the body-surface area), overlapping Stevens–Johnson syndrome and toxic epidermal necrolysis (skin detachment of 10 to 29 percent of the body-surface area), or toxic epidermal necrolysis (widespread detachment of the epidermis, involving 30 percent or more of the body-surface area). Histologic features, which help differentiate these processes from other blistering diseases but not from each other, were not used for classification.

Without any information on exposures and with the use of explicit rules, an "index day" was designated as the date of the onset of symptoms or signs that progressed within three days to definite erosions or blisters of the skin or mucous membranes. When a more protracted course or more ambiguous prodromes were noted, an "earlier index day" was also chosen.

A total of 492 potential case patients were recruited as of June 30, 1993. The review excluded 20 patients and classified 60 as having possible disease. Only patients with probable (n = 126) or definite (n = 286) disease were assessed further. Of these 412 patients (84 percent of potential case patients), 12 were excluded because an index

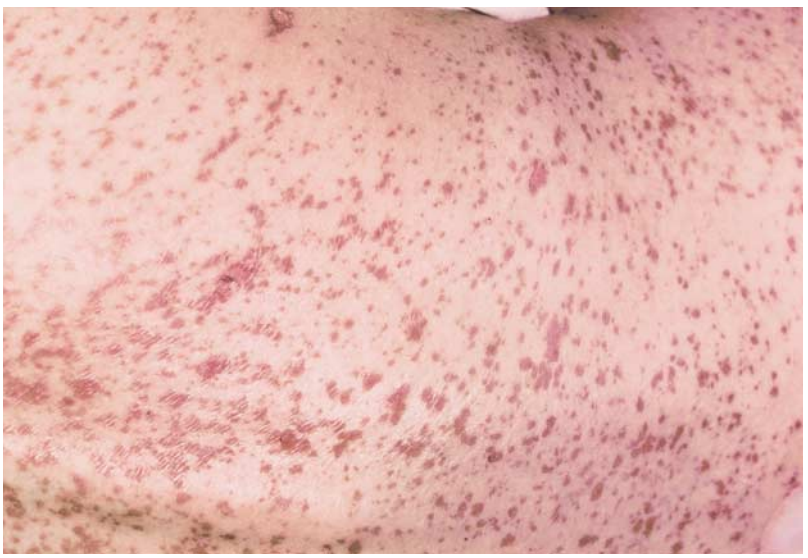

Figure 2. Typical Pattern of Stevens–Johnson Syndrome.
Blisters develop on widespread purpuric macules.

day could not be determined for them and 155 were categorized as having erythema multiforme major (60 patients) or ambiguous diagnoses of erythema multiforme major or Stevens–Johnson syndrome (95 patients), leaving 245 that were included in the analyses.

The study included 121 case patients from France, 57 from Italy, 49 from Germany, and 18 from Portugal. Eighty-nine were classified as having Stevens–Johnson syndrome, 76 as having overlapping Stevens–Johnson syndrome and toxic epidermal necrolysis, and 80 as having toxic epidermal necrolysis. Biopsy data were available for 141 patients (58 percent), relevant clinical photographs for 196 (80 percent), and either biopsy data or photographs for 219 (89 percent). A single index day was determined for 181 patients (74 percent); 64 (26 percent) also had an earlier possible index day. The median interval from the index day to hospitalization was two days. For the 64 patients with earlier index days, the median interval was five days.

Control Subjects

Control subjects were patients admitted to the same hospitals for an acute condition or for an elective procedure not suspected of being related to medication use (e.g., traumatic injuries, acute infections, abdominal emergencies excluding those related to peptic ulcers, and hernia repair) within one month of the case patients with whom they were matched. Patients with chronic disorders were eligible if hospitalized for an unrelated acute disease but not if admitted for an acute exacerbation of a chronic disease.

Admission and discharge diagnoses, without information on medications, were reviewed to determine the eligibility of the controls. The day of the first symptom in cases of acute conditions, or the day of admission for elective procedures, was defined as the index day. Among 1332 controls who were interviewed, 151 (11 percent) were excluded because their diagnoses were considered unsuitable; 34 (3 percent) could not be analyzed because their index days were unknown or the interval from the index day to hospitalization was more than 21 days. To maximize the power of the study, all 1147 eligible controls were used. As a result, certain characteristics were not similar among controls and case patients (median age, 33 vs. 41 years, and male patients, 50 percent vs. 44 percent, respectively). A total of 42 percent of the controls were admitted for trauma, 27 percent for infections, and 31 percent for abdominal emergencies or other conditions.

Data Collection and Drug Inquiry

A questionnaire was used to gather information on medical history, demographic characteristics, and exposures other than to drugs. Information on drug use was collected for the four weeks preceding hospitalization. Patients were first read a list of indications for potential treatment, followed by a list of brand names for drugs of interest. The latter included brands covering 80 to 90 percent of each national market for drugs previously suspected of causing Stevens–Johnson syndrome or toxic epidermal necrolysis. For each drug taken, the timing of use, dose, indication, previous exposure, and previous adverse reactions were documented. For children and patients too ill to be interviewed, family members and medical records provided this information.

Statistical Analysis

On the hypothesis that a drug does not induce a reaction when no longer present in the body, we restricted the window for relevant exposure to seven days before the index day for most drugs. The exposure window was extended to 14 days for agents with elimination half-lives between 24 and 48 hours (e.g., oxicam NSAIDs, chlormezanone, and allopurinol) and to 3 weeks for phenobarbital (with a half-life of about 100 hours).

In addition to overall exposure, the duration of therapy was evaluated, because of the clinical observation that severe skin reactions usually occur within weeks of a patient's starting a drug. Recently initiated use was defined as therapy started within two months of the index day. If the number of users was large enough, individual drugs were examined; otherwise, drugs were grouped on the basis of similar chemical structures or pharmacologic effects (e.g., hypoglycemic sulfonylureas and thiazide diuretic agents).

The data were analyzed with the use of standard case–control methods for the estimation of crude relative risks (unadjusted odds ratios), with 95 percent confidence intervals.[14] For drugs with "infinite" crude relative risks, the median unbiased estimate was calculated according to the method of Hirji et al.,[15] and the lower limit of the confidence interval was calculated according to the method of Thomas.[16] For drugs being taken by at least three case patients and controls, we used multivariate analysis to consider simultaneously the effects of potential confounding factors, using unconditional multiple logistic regression.[17] The models included demographic factors and other medical factors previously hypothesized as risk factors, including radiotherapy, with 13 case patients (5 percent) and 13 controls (1 percent); collagen vascular disease, with 14 (6 percent) and 7 (0.6 percent); infection with the human immunodeficiency virus, with 18 (7 percent) and 2 (0.2 percent); and recent herpes infection, with 15 (6 percent) and 46 (4 percent). Terms for other drugs suspected of being associated with Stevens–Johnson syndrome or toxic epidermal necrolysis and for all remaining drugs were included in the models.

Excess risk (the incidence per week of use attributable to the exposure) was estimated on the basis of the relative risk, the etiologic fraction, and annual incidence.[18] On the basis of data from the German registry, the incidence of Stevens–Johnson syndrome and toxic epidermal necrolysis was estimated as 1.5 cases per million person-years.[19] Multivariate relative risks were used when available; otherwise, the crude estimates or the median unbiased estimates were used.

Results

Within the week preceding the index day for each subject, 223 of 245 case patients (91 percent) and 563 of 1147 controls (49 percent) used at least one drug. One or more drugs previously suspected of causing Stevens–Johnson syndrome or toxic epidermal necrolysis had been taken by 144 case patients (59 percent) and 167 controls (15 percent). Because the rates of exposure to drugs suspected of causing these conditions (adjusted for age, sex, and region) were similar for each subgroup (those with Stevens–Johnson syndrome, 66 percent; those with overlapping Stevens–Johnson syndrome and toxic epidermal necrolysis, 56 percent; and those with toxic epidermal necrolysis, 59 percent), all case patients were analyzed together.

Table 1 shows risk estimates for drugs previously suspected of causing Stevens–Johnson syndrome or toxic epidermal necrolysis. Antibacterial sulfonamides were the most strongly associated with the conditions, with a crude relative risk of 172 (95 percent confidence interval, 75 to 396). Trimethoprim–sulfamethoxazole accounted for 69 percent of the cases, with a median unbiased relative-risk estimate of 160. Among nonsulfonamide antibiotics, aminopenicillins (multivariate relative risk, 6.7), quinolones (10), cephalosporins (14), tetracyclines (8.1), and imidazole antifungal agents (crude relative risk, 24) were significantly associated with the conditions. When recent infection was included in the model, relative risks associated with the use of nonsulfonamide antibiotics decreased somewhat, but all remained significant, ranging from 4.5 to 11. The anticonvulsant agents phenytoin, valproic acid, phenobarbital, and carbamazepine all had significant multivariate relative risks, ranging from 8.3 to 12. Among NSAIDs, only oxicam derivatives were significantly associated with the diseases (multivariate relative risk,

Table 1. Risk Estimates for Drugs Previously Suspected of Being Associated with Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis.*

Drug	Case Patients (N = 245)	Controls (N = 1147)	Crude Relative Risk (95% CI)	Multivariate Relative Risk (95% CI)†
	no. (%) exposed			
Sulfonamides	32 (13)	1 (0.1)	172 (75–396)	NC
Trimethoprim–sulfamethoxazole	22 (9)	0	∞‡ (28–∞)	NC
Sulfadiazine	5 (2)	0	∞ (4.3–∞)	NC
Sulfasalazine	3 (1)	0	∞ (1.9–∞)	NC
Other	2 (1)	1 (0.1)		
Aminopenicillins§	15 (6)	12 (1)	6.2	6.7 (2.5–18)
Quinolones¶	11 (4)	5 (0.4)	11	10 (2.6–38)
Cephalosporins‖	14 (6)	3 (0.3)	23	14 (3.2–59)
Macrolides**	6 (2)	5 (0.4)	5.7	1.6 (0.2–13)
Tetracyclines††	5 (2)	4 (0.3)	6.0	8.1 (1.5–43)
Imidazole antifungal agents‡‡	5 (2)	1 (0.1)	24 (5.5–104)	NC
Phenobarbital§§	28 (12)	9 (0.9)	15	8.7 (3.2–23)
Carbamazepine	13 (5)	6 (0.5)	11	12 (3.5–38)
Phenytoin	8 (3)	3 (0.3)	13	8.3 (1.5–45)
Valproic acid	10 (4)	4 (0.3)	12	8.3 (1.8–40)
Oxicam NSAIDs¶¶	15 (6)	4 (0.3)	18	22 (6.2–74)
Piroxicam	9 (4)	4 (0.3)‖‖	11	12 (3.1–45)
Tenoxicam	6 (2)	1 (0.1)‖‖	28 (6.9–113)	NC
Propionic acid NSAIDs***	12 (5)	13 (1)	4.5	1.7 (0.6–5.3)
Diclofenac	5 (2)	9 (0.8)	2.6	2.8 (0.7–10)
Salicylates	32 (13)	80 (7)	2.0	1.3 (0.7–2.4)
Pyrazolone derivatives	7 (3)	16 (1)	2.1	2 (0.6–6.8)
Dipyrone	4 (2)	11 (1)	1.7	1.4 (0.2–9.2)
Acetaminophen				
France	26 (21)	72 (13)	1.8	0.6 (0.2–1.3)
Other countries	22 (18)	16 (3)	8.0	9.3 (3.9–22)
Allopurinol¶¶	13 (5)	11 (1)	5.6	5.5 (2.0–15)
Chlormezanone¶¶	13 (5)	1 (0.1)	62 (21–188)	NC

*The possible association of these drugs with these conditions has been reported in previous studies.[1,2,4-10] CI denotes confidence interval.

†NC denotes not calculated; multivariate relative risks were estimated only in cases in which there were at least three exposed case patients and controls (see the Methods section).

‡Median unbiased estimate, 160.

§This category includes amoxicillin (10 case patients and 9 controls), bacampicillin (4 and 1), and ampicillin (1 and 2).

¶This category includes ciprofloxacin (3 case patients and 2 controls), pefloxacin (3 and 0), ofloxacin (3 and 1), pipemidic acid (2 and 0), and norfloxacin (0 and 2).

‖This category includes cefadroxil (5 case patients and 1 control), cefaclor (2 and 0), ceftriaxone (2 and 0), cefixime (1 and 1), cefpodoxime (1 and 1), cefatrizine (1 and 0), cefroxadine (1 and 0), and cefotaxime (1 and 0).

**This category includes roxithromycin (2 case patients and 2 controls), spiramycin (2 and 0), erythromycin (2 and 0), josamycin (0 and 2), and pristinamycin (0 and 1).

††This category includes doxycycline (5 case patients and 3 controls) and tetracycline (0 and 1).

‡‡This category includes fluconazole (3 case patients and 1 control), ketoconazole (1 and 0), and miconazole (1 and 0).

§§Used 1 to 21 days before the index day by 236 case patients and 1040 controls.

¶¶Used 1 to 14 days before the index day by 245 case patients and 1112 controls.

‖‖One control used both piroxicam and tenoxicam.

***This category includes ketoprofen (5 case patients and 6 controls), naproxen (3 and 4), tiaprofenic acid (2 and 1), and ibuprofen (2 and 2).

22). The upper 95 percent confidence limits for propionic acid derivatives and for diclofenac make it impossible to rule out some increase in risk, but the risk with oxicam NSAIDs was significantly higher ($P = 0.009$ and $P = 0.02$, respectively). Other drugs significantly associated with the conditions included allopurinol (multivariate relative risk, 5.5) and chlormezanone (crude relative risk, 62).

Among analgesics, salicylates and pyrazolone derivatives did not appear to be associated with the conditions. For acetaminophen there were regional differences. No association was seen in France, with a multivariate relative risk of 0.6 (95 percent confidence interval, 0.2 to 1.3). In other countries, there was a significantly positive association (9.3; 95 percent confidence interval, 3.9 to 22), which remained when the analysis was confined to subjects with fever.

When we repeated the analyses using the earlier index days established for some subjects, there were no substantial changes in the results (data not shown).

Many commonly prescribed drugs (those with a prevalence of use among the controls of at least 1 percent) were not associated with Stevens–Johnson syndrome or toxic epidermal necrolysis (Table 2), with relative risks close to 1.0 and upper 95 percent confidence limits of 3.0 or below. For some drugs not significantly associated with the diseases, the upper bounds of the confidence interval did not exclude moderate increases in risk.

A significant association was observed for corticosteroids. The estimate of crude relative risk was considerably higher than the estimate of multivariate relative risk (12 vs. 4.4). This difference was explained by confounding by several factors, including the use of antiinfective and anticonvulsant agents, a history of radiotherapy, and a history of collagen vascular disease. To attempt to distinguish the effects of corticosteroids from those of underlying diseases, we repeated the analysis with the subjects with a history of cancer or collagen vascular disease excluded. The estimates of multivariate relative risk were 4.9 (95 percent confidence interval, 2.1 to 11) and 5.2 (2.2 to 12), respectively.

Some drugs associated with Stevens–Johnson syndrome and toxic epidermal necrolysis are usually prescribed for long-term therapy of other conditions. For these drugs, the median duration of use was markedly lower for case patients than for controls. As shown in Table 3, the risks were greatly elevated for patients who had recently started therapy (≤2 months' duration) with anticonvulsants, allopurinol, oxicam NSAIDs, and corticosteroids, ranging from 52 to infinity (median unbiased estimates, 25 to 90). Significantly elevated but lower relative risks remained for the long-term use of phenobarbital (5.8) and valproic acid (7.3).

Estimates of excess risk with drugs associated with the conditions are shown in Table 4, expressed as the number of cases attributable to the drug per million users in one week. These ranged from a low of 0.2 per million for aminopenicillins to a high of 4.5 per million for sulfonamides.

Discussion

We studied Stevens–Johnson syndrome and toxic epidermal necrolysis, two rare but severe blistering

Table 2. Risk Estimates for Other Drugs in Common Use.*

Drug	Case Patients (N = 245)	Controls (N = 1147)	Crude Relative Risk	Multivariate Relative Risk (95% CI)
	no. (%) exposed			
Contraceptive pills†	11 (19)	53 (20)	1.0	0.4 (0.1–1.5)
Benzodiazepines	28 (11)	84 (7)	1.6	0.3 (0.1–0.7)
Phenothiazines	11 (5)	16 (1)	3.3	1.6 (0.5–5.4)
Sulfonylureas‡	4 (2)	13 (1)	1.4	0.7 (0.1–3.2)
Thiazide diuretics	17 (7)	44 (4)	1.9	1.4 (0.5–2.8)
Hydrochlorothiazide	12 (5)	33 (3)	1.7	1.2 (0.3–4.6)
Other diuretic agents	19 (8)	55 (5)		
Amiloride	5 (2)	15 (1)	1.6	1.1 (0.2–5.2)
Furosemide	4 (2)	16 (1)	1.2	0.3 (0.05–1.6)
Fibrate antihyperlipids§	10 (4)	21 (2)	2.3	1.0 (0.4–2.8)
Angiotensin-converting–enzyme inhibitors	14 (6)	35 (3)	1.9	1.2 (0.5–2.8)
Captopril	6 (2)	23 (2)	1.2	0.9 (0.2–3.1)
Calcium-channel blockers	16 (7)	38 (3)	2.0	1.5 (0.7–3.5)
Nifedipine	8 (3)	14 (1)	2.7	1.4 (0.4–4.6)
Beta-blockers	8 (3)	23 (2)	1.7	1.4 (0.4–4.2)
Other antihypertensive and vasodilating agents	20 (8)	48 (4)		
Isosorbide	8 (3)	19 (2)	2.0	1.0 (0.3–3.4)
Digitalis glycosides	9 (4)	16 (1)	2.7	0.8 (0.2–2.7)
H_1 antihistamines	23 (9)	36 (3)	3.2	1.7 (0.8–3.7)
H_2 antihistamines	12 (5)	20 (2)	2.9	1.5 (0.5–4.2)
Biguanides¶	4 (2)	15 (1)	1.2	0.8 (0.2–3.0)
Levothyroxine	6 (2)	17 (2)	1.7	0.6 (0.1–2.5)
Corticosteroids	35 (14)	16 (1)	12	4.4 (1.9–10)

*Drugs with a prevalence of use among the controls of at least 1 percent. CI denotes confidence interval.

†Among female patients 15 to 45 years of age (57 case patients and 270 controls).

‡This category includes glyburide (1 case patient and 11 controls), gliclazide (1 and 1), glipizide (1 and 0), tolbutamide (1 and 0), and glibornuride (0 and 1).

§This category includes fenofibrate (7 case patients and 10 controls), bezafibrate (3 and 5), ciprofibrate (0 and 3), gemfibrozil (0 and 2), and etofibrate (0 and 1).

¶This category includes phenformin (3 case patients and 4 controls), metformin (1 and 7), metformin embonate (0 and 3), and metformin chlorophenoxyacetate (0 and 1).

mucocutaneous diseases that, according to our disease definitions, share common clinical and histopathological features but vary in the extent of epidermal detachment.[3,6] Both are frequently associated with drug use.[1,2,4-11]

This large case–control study determined with substantial precision the risks of toxic epidermal necrolysis and Stevens–Johnson syndrome associated with the use of the most commonly prescribed drugs. It confirms that the use of antibacterial sulfonamides, oxicam NSAIDs, chlormezanone, anticonvulsant agents, and allopurinol is associated with substantial relative increases in the risk of toxic epidermal necrolysis and Stevens–Johnson syndrome. Significant associations were also observed for many antibiotics and, unexpectedly, for corticosteroids. With all drugs associated with the conditions, the excess risks were low. The highest rate, for sulfonamides, was 4.5 cases per million users per week. For many drugs, the risk of Stevens–Johnson syndrome and toxic epidermal necrolysis was highest in the first weeks of use. This confirms the clinical impression and has implications for understanding the mechanisms of these disorders and for therapy.

Sulfonamides have often been implicated as a cause of Stevens–Johnson syndrome and toxic epidermal necrolysis.[5,7-10,20-22] In the present study, trimethoprim–sulfamethoxazole was the sulfonamide most frequently used by case patients. Despite their structural relations to antibacterial sulfonamides, thiazide diuretics and sulfonylureas were not associated with increased risks.

Many antibiotics have previously been implicated in at least a few case reports.[1,2,4,5,8,9] Because fever may begin a few days before the skin manifestations, the reaction might be related to infection rather than to the drugs.[4] We found significant associations for most classes of antibiotics, including cephalosporins, quinolones, aminopenicillins, tetracyclines, and imidazole antifungal agents. An association for all antiinfective drugs could suggest some confounding by indication. The associations remained significant, with lower point estimates, when a term for recent infection was included in the multivariate model. This result and the reports of cases related to prophylactic administration of long-acting sulfonamides[20-22] suggest that antibiotics and not infection cause the reaction.

Among NSAIDs, butazone derivatives (phenylbutazone and oxyphenbutazone) have long been implicated.[7] Because these drugs are now seldom used, no information about them was available for the current study. Oxicam derivatives were also suspected.[23] Isoxicam was withdrawn from the market in France after having been associated with 13 cases of toxic epidermal necrolysis.[8] The two currently marketed oxicams, piroxicam and tenoxicam, were significantly associated, and risks were significantly higher for them than for diclofenac and propionic acid derivatives. The risks were linked to recently initiated therapy. When the analysis was restricted to treatment of two months or less, the risk increased with oxicams but not with propionic acid derivatives. The prevalence of the use of other NSAIDs was too low to permit an analysis of individual drugs.

Severe adverse cutaneous reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis, have long been associated with the use of aromatic anticonvulsant drugs (phenobarbital, phenytoin, and carbamazepine).[1,2,24,25] The current study demonstrated that valproic acid, often viewed as safer with respect to cutaneous reactions,[25] had a significant risk that was similar to that of aromatic anticonvulsants. For all anticonvulsants, the risk was greatest in the first two months of treatment, although some increased risk persisted among long-term users of phenobarbital and valproic acid.

Allopurinol, which is most often administered for long periods, is frequently cited as a cause of Stevens–Johnson syndrome and toxic epidermal necrolysis.[5,7,9,26] The risk is not constant over time. The relative risk

Table 3. Estimates of Relative Risk According to the Duration of Therapy.

Drug	Duration (mo)	Case Patients (N = 245)	Controls (N = 1147)	Crude Relative Risk	(95% CI)*
Sulfonamides	≤2	29	1	156	(66–367)
	>2	2	0	∞	(1.5–∞)
		1†			
Aminopenicillins	≤2	15	12	6.2	(3.1–12)
	>2	0	0		
Quinolones	≤2	11	2	18	(7–46)
	>2	0	2	0	(0–26)
			1†		
Cephalosporins	≤2	14	3	23	(9.7–55)
	>2	0	0		
Phenobarbital	≤2	18	2	45	(19–108)
	>2	7	6	5.8	(2.2–82)
		3†	1†		
Carbamazepine	≤2	13	0	∞‡	(19–∞)
	>2	0	6	0	(0–3.2)
Phenytoin	≤2	8	0	∞§	(11–∞)
	>2	0	3	0	(0–12)
Valproic acid	≤2	4	0	∞¶	(4.3–∞)
	>2	6	4	7.3	(2.5–22)
Oxicam NSAIDs	≤2	15	1	72	(25–209)
	>2	0	2	0	(0–47)
			1†		
Propionic acid NSAIDs	≤2	10	9	5.4‖	(2.4–12)
	>2	2	4	2.4	(0.4–13)
Allopurinol	≤2	11	1	52	(16–167)
	>2	1	9	0.5	(0.1–4)
		1†	1†		
Chlormezanone	≤2	13	1	62	(21–188)
	>2	0	0		
Corticosteroids	≤2	20	2	54	(23–124)
	>2	15	14	5.8**	(3–11)

*CI denotes confidence interval.

†The duration of use was unknown.

‡Median unbiased estimate, 90.

§Median unbiased estimate, 53.

¶Median unbiased estimate, 25.

‖Multivariate estimate, 2.6 (95 percent confidence interval, 0.7 to 9.4).

**Multivariate estimate, 1.6 (95 percent confidence interval, 0.6 to 4.8).

with any use (5.5) underestimates the risk during the first two months of therapy (52) and overestimates the risk with long-term therapy (0.5).

Chlormezanone is a minor tranquilizer not related to the benzodiazepines that has muscle-relaxing properties and sedative effects.[27] Frequently prescribed in Europe together with NSAIDs and analgesics, chlormezanone has been suspected of inducing severe cutaneous reactions.[7,8] The results of our study indicate a high relative risk.

Since Stevens–Johnson syndrome and toxic epidermal necrolysis are probably mediated immunologically[1,2] and corticosteroids prevent other types of drug reactions,[28] the significant increase in risk associated with exposure to corticosteroids was surprising. Topical[29] and systemic[30] corticosteroids, however, can induce contact dermatitis and other skin reactions. Toxic epidermal necrolysis can occur in spite of high doses of systemic corticosteroids.[31,32] No explanation is apparent for the high risk we observed with recently initiated corticosteroid therapy. This association does not appear to be due to underlying diseases for which the drugs were sometimes used (e.g., collagen vascular diseases and brain tumors) or to the use of other drugs associated with Stevens–Johnson syndrome and toxic epidermal necrolysis. The relative risk remained significantly elevated when subjects with these factors were excluded.

Acetaminophen was not a significant risk factor in France. In contrast, the multivariate risk was 9.3 in other countries. The rates of use in the various countries were similar among case patients but quite different among controls: 13 percent in France as compared with 2.5 percent in the other countries (range, 1 to 4 percent). The annual sales of acetaminophen in France are 10 and 20 times those in Germany and Italy, respectively (Vesque D, UPSA laboratories: personal communication). In other studies in Italy[33] and France,[34] estimated acetaminophen use in controls was similar to that in ours. These findings support our observation about variation in use among controls. Acetaminophen is used mainly as an antipyretic in Italy, Germany, and Portugal and as an analgesic in France. Confining the analysis to subjects with fever, however, did not explain the difference in risk between countries. One hypothesis is that the prevalence of use in France is so high that repeated exposures could lead to either the selection of patients who do not react or the induction of tolerance. It has recently been suggested that people's past experience with NSAIDs decreases the overall risk of NSAID-associated bleeding in the upper gastrointestinal tract, perhaps because susceptible people select themselves out of the population at risk.[35]

The validity of the present study depends on many

Table 4. Estimates of Excess Risk with Drugs Associated with Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis.

Drug	Relative Risk*	Excess Risk†
Sulfonamides	172‡	4.5
Trimethoprim–sulfamethoxazole	160§	4.3
Aminopenicillins	6.7¶	0.2
Quinolones	10¶	0.3
Cephalosporins	14¶	0.4
Tetracyclines	8.1¶	0.2
Phenobarbital (≤2 mo)	45‡	1.2
Carbamazepine (≤2 mo)	90§	2.5
Phenytoin (≤2 mo)	53§	1.5
Valproic acid (≤2 mo)	25§	0.7
Oxicam NSAIDs (≤2 mo)	72‡	2.0
Allopurinol (≤2 mo)	52‡	1.5
Chlormezanone (≤2 mo)	62‡	1.7
Corticosteroids (≤2 mo)	54‡	1.5

*For drugs other than antiinfective agents, calculations were based on relative risks associated with short-term use.

†Excess risk is expressed as the number of cases of disease attributable to the drug per million users in one week.

‡Crude estimate.

§Median unbiased estimate.

¶Multivariate estimate.

factors, including the unbiased recruitment of case patients and controls and the accuracy of the information obtained about drug use. The study was designed to include all case patients admitted to hospitals participating in a surveillance network and to minimize possible recall bias about drug use. These methods should help ensure that rates of drug use among our controls were not substantially underestimated. The various prevalences of use in the various countries are concordant with the considerable heterogeneity of the European drug market.[36] The rates of drug use among our controls were similar to those found in previous European studies for aspirin,[33,34,37] NSAIDs,[33,37] acetaminophen,[33,34,37] benzodiazepines,[34,38] and oral contraceptives.[39] In addition, the many drugs for which we found relative risks close to 1.0 provide some measure of internal control and suggest that any residual recall bias could contribute only minimally to the large relative risks observed with other drugs. The remaining validity issue is the problem of confounding, especially by the concomitant use of multiple drugs. When the number of subjects permitted, this was taken into account by multivariate analysis. Relative risks based on crude comparisons should be considered less reliable, even if they are large and unlikely to be entirely explained by confounding.

An important perspective on Stevens–Johnson syndrome and toxic epidermal necrolysis as a public health issue is provided by the excess risks. Our results indicate that the highest risks are associated with antibacterial sulfonamides, with an excess risk of 4.5 cases per million exposed persons per week. These extremely low risks are consistent with the rarity of these diseases. Given the high morbidity and mortality associated with these conditions, however, prescribing physicians should still consider that alternative therapies have substantially lower excess risks.

APPENDIX

In addition to the study authors, the following investigators participated in the study:

France: B. Bégaud, A. Chaslerie, V. Legrain, and F. Penouil, Université de Bordeaux; B. Sassolas, Université de Brest; I. Alcaraz, H. Bergoend, E. Berteloot, and C. Marlier, Université de Lille; B. Ducros, D. Jullien, S. Lyonnet, L. Misery, and C. Stamm, Université de Lyon; N. Bassères, J.-J. Bonérandi, N. Cnudde, A. Raoux, and F. Roudil, Université de Marseille; C. Delavierre and E. Mansat, Université de Nantes; H. Assier, C. Bénabou, Z. El Wady, C. Raffin, and S. Slimani, Université Paris XII; M. Foret, Université de Poitiers; H. Bosser, E. Grosshans, and M. Sanchez, Université de Strasbourg; F. Sorbette, Université de Toulouse; and N. Julien, J.-P. Morère, D. Roger, and L. Vaillant, Université de Tours. *Germany:* B. Wegner, S. Baur, M. Körner, J. Mueller, U. Stocker, and K. Wieck, Dokumentationszentrum schwerer Hautreaktionen, Freiburg; R. Bruppacher, University of Basel; G. Kreutz, Bundesinstitut für Arzneimittel und Medizinprodukte, Berlin; T. Ruzicka, University of Düsseldorf; J. Ring and D. Vieluf, University of Hamburg; U. Schwabe and N. Victor, University of Heidelberg; G. Hopf and K.-H. Munter, Arzneimittelkommission der deutschen Ärzteschaft, Köln; U.-F. Haustein, University of Leipzig; K. Bork, University of Mainz; B. Przybilla, University of Munich; and H. Heilmaier, Bundesministerium für Forschung und Technologie, Munich. *Italy:* M. Cavaleri, Hospital of Albenga-Alassio; R. Filotico, University of Bari; F. Cusano, Hospital of Benevento; A. Tosti and C. Misciali, University of Bologna; G. Pasolini, Hospital of Brescia; A. Pinna, University of Cagliari; T. Di Prima, University of Catania; F. Arcangeli, Hospital of Cesena; A. Locatelli, Hospital of Como; S. Moretti and G. Palleschi, University of Florence; A. Virgili, University of Ferrara; G. Fenizi, Hospital of Foggia; A. Burroni and A. Pestarino, S. Martino and Galliera Hospitals of Genoa; F. Rongioletti, University of Genoa; G. Cannata, Hospital of Imperia; R. Betti, M.M. Polenghi, and S. Veraldi, University of Milan; E. Rossi and E. Gennari, Hospital of Monza; N. Balato, University of Naples; C. Veller Fornasa and S. Poletto, University of Padua; P. Perno, University of Perugia; A. Fanti, Hospital of Ravenna; S. Gatti, University of Rome; A. Farris, Hospital of Savona; P. Taddeucci, University of Siena; P. Puiatti and C. Solaroli, University of Turin; G. Magaton Rizzi, University of Trieste; and D. Schena, University of Verona. *Portugal:* M. Gonçalo and F. Neves, University of Coimbra; M. Dias, Hospital Curry Cabral, Lisbon; H. Melo, Hospital Desterro, Lisbon; M. Martins and F. Menses-Brandão, Hospital Sta. Maria, Lisbon; C. Lisboa, Hospital S. João, Porto; and G. Velho, Hospital Sto. Antonio, Porto.

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