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STUDY

Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome

Does Early Withdrawal of Causative Drugs Decrease the Risk of Death?

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Background: Withdrawal of the drug(s) that cause severe cutaneous adverse reactions is usually recommended without proof that it alters the course of those reactions.

Objective: To determine whether the timing of causative drug withdrawal is related to the prognosis of patients with toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS).

Design: A 10-year observational study (January 1, 1987, through October 30, 1997) of patients admitted to a dermatological intensive care unit, using binary logistic regression analysis.

Setting: A single referral unit in a university hospital.

Patients: Consecutive sample of 203 patients with TEN or SJS. Exclusion criteria included causative drug undetermined, lack of information on disease evolution, the date of causative drug(s) withdrawal, or the date when the first definite sign of TEN or SJS appeared.

Main Outcome Measure: Death before hospital discharge.

Results: One hundred thirteen patients were included; 74 had TEN and 39 had SJS; 20 died. The drug causing TEN or SJS was withdrawn early in 64 patients and late (after the first definite sign of TEN or SJS) in 49 patients. After adjustment for confounding variables (age, maximum extent of detachment, admission year, human immunodeficiency virus status), our model showed that the earlier the causative drug was withdrawn, the better the prognosis (odds ratio, 0.69 for each day; 95% confidence interval, 0.53-0.89). Patients exposed to causative drugs with long half-lives had an increased risk of dying (odds ratio, 4.9; 95% confidence interval, 1.3-18.9). The variables did not interact.

Conclusions: Prompt withdrawal of drug(s) that are suspected to cause SJS or TEN may decrease mortality. Prompt withdrawal of causative drugs should be a priority when blisters or erosions appear in the course of a drug eruption.

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ADVERSE DRUG effects occur frequently enough to be a public health concern.[1] Cutaneous adverse reactions to drugs are among the most frequent complications of therapy. One of the most severe cutaneous reactions to drug therapy is toxic epidermal necrolysis (TEN), a rare disease that results in skin eruptions resembling burns and is characterized by extensive epidermal loss.[2-5]

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Toxic epidermal necrolysis is often heralded by fever, sore throat, cough, and burning eyes for 1 to 3 days. The cutaneous eruption usually begins as poorly defined erythematous macules with darker purpuric centers that tend to merge. Within a few days, sometimes within a few hours, flaccid blisters and a sheet-like epidermal detachment appear and extend over the body, and the patient exhibits a positive Nikolsky sign. Mucous membrane erosions are present in nearly all patients with TEN, sometimes preceding skin lesions for several days. The epithelium of the trachea, bronchi, or gastrointestinal tract may also be involved, increasing morbidity.[2-5]

The relationship of TEN with Stevens-Johnson Syndrome (SJS) and erythema multiforme has been an issue of confusion and debate. There is growing evidence that SJS and TEN constitute a spectrum of disease that is distinct from erythema multiforme but with similar histopathologic characteristics, overlapping patients, and cases of transition from SJS to TEN.[4,6-8] Patients within this spectrum have been classified according to the morphologic features of their lesions and the extent of detached and detachable epidermis. Cases with widespread purpuric

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PATIENTS AND METHODS

From January 1, 1987, through October 30, 1997, 203 patients with TEN or SJS that was not related to graft-vs-host disease were admitted to the Dermatological Intensive Care Unit at Hôpital Henri Mondor, Créteil, France. All patients were asked at admission about drug intake and dates of onset and withdrawal with a standardized questionnaire used routinely at our center. All patients received treatment for symptoms; corticosteroids were not used for therapy. After the formulation of our hypothesis, we performed a retrospective analysis of each patient's medical records.

We selected those patients who had clearly recorded evidence of the following: (1) history of taking causative drug(s), (2) date(s) when causative drug(s) administration was stopped, (3) date when the first definite sign of TEN or SJS occurred, and (4) disease evolution. Patients who were diagnosed according to published clinical criteria were determined to have TEN or SJS.[7] Histologic confirmation of the diagnosis was performed in all patients.

THE FIRST DEFINITE SIGN OF TEN OR SJS

The first definite sign of TEN or SJS was defined as the appearance of the first blister or erosion on the skin or mucous membrane that was not explained by another cause.[9]

CAUSATIVE DRUG

A drug was determined to have caused a patient's disease by an adaptation of the method used by the official French Drug Surveillance Network.[11,14] A score of 0 to 4 was attributed to each drug that was taken by the patient during the month before the first cutaneous sign of TEN or SJS. This score was related to the timing of drug administration and the onset of disease. Drugs with a score of 2 or higher were considered to be potentially causative. The drug with the highest score was considered the causative drug. When several drugs had the same score for a single patient, the drug most often cited in the literature as causing TEN or SJS was considered the causative drug. When more than one drug could be considered causative, we included only those patients (n = 6) for whom all causative drugs were withdrawn on the same day and had similar elimination half-lives.

CATEGORIZATION OF CAUSATIVE DRUGS

To explore the hypothesis of confounding between the elimination half-lives of drugs and the severity of underlying diseases for which they had been prescribed, we also grouped causative drugs into 4 arbitrary categories: drugs commonly used for nonsevere diseases (eg, analgesics, anti-inflammatory agents, antidepressants, and drugs for hyperlipidemia), anti-infectious drugs, antiepileptic drugs, and other drugs (eg, sulfasalazine, dapsone, and allopurinol).

TIMING OF DRUG WITHDRAWAL

Patients were determined to have stopped drug administration early if the last dose of the causative drug was administered no later than the same day that a definite sign of TEN or SJS appeared. If the drug was continued after that day, patients were determined to have stopped drug administration late. For the logistic regression model, we considered day 0 to be 20 days before the first definite sign of TEN or SJS; for each patient we counted the number of days from that date to the day when causative drug administration was stopped.

CAUSATIVE DRUG ELIMINATION HALF-LIFE

Causative drug elimination half-life data were obtained from standard pharmacology textbooks.[15,16] We classified a causative drug as having a short half-life if its elimination half-life was less than 24 hours. A causative drug with a half-life of 24 hours or longer was considered to have a long half-life.

We split the data file into 4 groups, taking into account the timing of drug withdrawal (early or late) and the half-life of the causative drug (short or long). We used one-way analysis of variance (ANOVA) to evaluate the homogeneity of other variables in these groups. Considering a binary response (dead or alive), we applied a binary logistic regression model to the data to evaluate the effect of each of the following variables: timing of drug withdrawal (in days vs early or late), causative drug half-life (in hours vs short or long), age (years), maximum skin detachment (percentage of body surface area), HIV status, and year of admission. Significantly associated variables were included in the model until we determined the best-fitting model. An analysis of possible effect modifiers included in the model showed that they had no significant effect; therefore, we ruled out interaction among variables, and 95% confidence intervals (CIs) of the results were calculated. Data analysis was performed using SPSS for Windows (version 7.5; SPSS Inc, Chicago, Ill).

macules and epidermal detachment below 10% are called SJS. Those with cutaneous detachment between 10% and 30% are called "transitional SJS-TEN," and those with more than 30% epidermal detachment are designated TEN.[7] Both diseases are primarily, if not solely, caused by drugs.[3,4,9]

Approximately 30% of patients with TEN die of infections or pulmonary complications. The main known clinical prognosis factors are age and the extension of the epidermal detachment.[4,10] Patients with SJS and SJS-TEN have a better prognosis. Previous investigations have been unable to find a relationship between causative drugs and prognosis.[11]

From a practical viewpoint, a drug eruption often starts as a morbilliform rash. Most often it has a benign course and does not progress. Several clinical findings are indicative of a severe drug reaction. Among them are markers of TEN or SJS, such as mucous membrane erosions, blisters or epidermal detachment, and a Nikolsky sign.[4] Even when the presence of these signs tells us that TEN or SJS is starting, it is usually impossible to distinguish between them, since the final extent of detached epidermis is their distinguishing feature.

In judgments regarding discontinuation of a drug for a patient with a drug eruption, use of the risk-

Table 1. Population Studied*

	Stopped Drug		Continued Drug	
	Short Half-life (n = 44)	Long Half-life (n = 20)	Short Half-life (n = 42)	Long Half-life (n = 7)
Age, y†	45.4 (20.6)	37.6 (14.0)	41.6 (18.9)	34.7 (14.7)
Sex, No. of patients				
Male	28	7	24	3
Female	16	13	18	4
Maximum skin detachment, % of body surface†	22.9 (18.1)	31.4 (27.7)	25.3 (24.5)	22.9 (18.9)
Diagnosed with TEN, No. (%)	28 (64)	14 (70)	27 (64)	5 (71)
Diagnosed with HIV, No. (%)	4 (9)	2 (10)	9 (21)	1 (14)
Deaths, No. (%)	2 (5)	5 (25)	11 (26)	2 (29)

*TEN indicates toxic epidermal necrolysis; HIV, human immunodeficiency virus.

†Values are mean (SD).

benefit ratio has been advocated,[12] and a "go-through" method has been accepted for some situations, particularly in persons infected with human immunodeficiency virus (HIV).[13] However, this decision is not based on firm knowledge because, as far as we know, the risk of a late withdrawal of the causative drug has never been evaluated.

Our aim was to determine whether the timing of causative drug withdrawal was related to mortality in patients with SJS or TEN.

RESULTS

From the initial series of 203 patients, 113 were included in the study (**Table 1**). The causes for exclusion of patients were the absence of a causative drug according to our definition (n = 63), the lack of a recorded date when the causative drug(s) administration was stopped (n = 19), the presence of several causative drugs with different half-lives or causative drugs that were withdrawn at different times (n = 7), and the absence of recorded disease evolution (n = 1). Twenty-eight of the excluded patients died.

Among the 113 patients included in our study, 74 had TEN and 39 had SJS, and 20 died—a death rate lower than that among the patients who were excluded from analysis ($P = .03$). The causative drug was withdrawn early in 64 patients and late (after the first definite sign of TEN or SJS) in 49. When patients were categorized in 4 groups according to early or late withdrawal of causative drugs with short or long half-lives, we could not find differences among the groups by mean age (ANOVA, $P = .31$) or mean maximum epidermal detachment (ANOVA, $P = .56$). Patients who stopped the administration of the causative drugs early had a lower death rate (7/64 [11%] vs 13/49 [27%]; $P = .046$ by χ^2 analysis). This was most apparent for patients with disease caused by drugs with short half-lives; their death rates were 5% (2/44) when the causative drug was withdrawn early and 26% (11/42) when it was stopped late ($P = .01$ by χ^2 analysis). For drugs with long half-lives, the death rates were similar whether the causative drug was withdrawn early or late.

Table 2. Half-lives of Causative Drugs

Drug	No. of Patients Exposed	Half-life, h*
Trimethoprim plus sulfamethoxazole	22	11/10
Sulfadiazine	15	13
Carbamazepine	12	20
Allopurinol	10	1-20
Diclofenac sodium	3	1.5
Valproic acid	3	11.5
Amoxicillin plus clavulanate potassium	2	1
Ceftriaxone sodium	2	8
Sulfasalazine	2	10
Ciprofloxacin	1	5
Clarithromycin	1	4
Clindamycin	1	2.5
Enalapril maleate	1	11
Fenofibrate	1	20
Fluvoxamine maleate	1	16
Gemfibrozil	1	1.5
Ibuprofen	1	2
Ketoconazole	1	8
Naproxen	1	13.5
Niflumic acid	1	5
Norfloxacin	1	3.5
Perfloxacin	1	12
Sulfaguanidine	1	10 (?)†
Colchicine (1 h)-allopurinol (1-20 h)‡	1	
Chlormezanone	6	24
Phenobarbital	6	95
Piroxicam	4	50
Dapsone	1	28
Sulfadoxine plus pyrimethamine (Fansidar)	2	60/96
Fluconazole	1	30
Lamotigrine	1	29
Paroxetine	1	24
Chlormezanone (24 h)-piroxicam (50 h)‡	2	
Chlormezanone (24 h)-tenoxicam (70 h)‡	1	
Fluconazole (30 h)-pyrimethamine (96 h)‡	1	
Perindopril (50 h)-phenobarbital (95 h)‡	1	

*Less than 24 hours was considered short.

†Because only 10% to 20% of ingested amounts of sulfaguanidine are absorbed, the behavior of this drug in plasma has not been studied in humans but is considered to be similar to that of sulfamethoxazole.[17]

‡In cases with 2 suspected causative drugs with similar half-lives, the drugs were withdrawn simultaneously.

There were many causative drugs (**Table 2**). After binary logistic regression model analysis was performed without considering any other variables, none of the following groups showed a significantly increased risk of death when compared with drugs commonly used for nonsevere diseases (n = 24): anti-infectious drugs (n = 52; odds ratio [OR], 0.97; 95% CI, 0.37-2.54), antiepileptic drugs (n = 23; OR, 1.15; 95% CI, 0.54-2.47), and sulfasalazine-dapsone-allopurinol (n = 14; OR, 0.46; 95% CI, 0.13-1.52).

Binary logistic regression model analysis of our data confirmed the significance of age and maximum epidermal detachment for predicting disease outcome. In addition, it showed that early withdrawal of the causative drug was associated with a better prognosis (OR, 0.69 for each day; 95% CI, 0.53-0.89) and that using drugs

Table 3. Maximum Likelihood Fit of a Binary Logistic Regression Model to Mortality Data

Factor	Odds Ratio (95% Confidence Interval)
Age, y	1.05 (1.01-1.08)
Percentage of epidermal detachment	1.03 (1.01-1.06)
Stopping the drug early (for each day before blisters and erosions)	0.69 (0.53-0.89)
Drug with half-life ≥24 h (vs half-life <24 h)	4.94 (1.30-18.91)

with a long half-life was associated with a poorer prognosis (OR, 4.94; 95% CI, 1.29-18.91) (**Table 3**); 95% CIs did not overlap 1 for any of the results. Our model was more closely fitted to the data than a model considering only age and maximum epidermal detachment (the primary prognosis factors that were previously accepted) to predict mortality. Different variables did not interact. In particular, the interaction effect of causative drug elimination half-life and the timing of causative drug withdrawal was not significant ($P = .26$). Human immunodeficiency virus status and the year that the patient was hospitalized were not associated with changes in prognosis.

Binary logistic regression model analysis performed to describe the risk of dying while considering only the day that the causative drug was stopped without other covariates provided significant results (number of days: OR, 1.28; 95% CI, 1.03-1.58). When other variables (ie, age, maximum skin detachment, and causative drug half-life) were included in the model, we observed that the model was improved and that the effect of the timing of drug withdrawal was reinforced (Table 3).

Binary logistic regression model analysis performed to describe the risk of dying while considering only the mean elimination half-life of the causative drug did not provide significant results (OR, 1.01; 95% CI, 0.99-1.02).

COMMENT

Our findings showed an increased rate of survival for patients with SJS or TEN who stopped taking causative drugs with short elimination half-lives early. To our knowledge, this finding has not been described before. In our series, 76% of cases occurred in patients taking drugs with short half-lives; therefore, our findings may have important practical implications for a majority of these patients.

The changes in prognosis that we identified cannot be explained by previously known prognosis factors, such as age and the maximum surface of skin detachment, or by presumably confounding variables, such as the year of admission or HIV status. The confounding effect of comorbid conditions that were not measured may not be very important, as suggested by the absence of changes in mortality by HIV status or by the type of causative drug used.

We believe there is a causal relationship between causative drug timing and mortality for several reasons. First, a causal relationship is plausible because the administration of causative drugs and disease progression follow a logical time sequence. Second, 2 different ways for decreasing the permanence of causative drugs in the body (ie, stopping the drug administration early and using drugs with a short elimination half-life) are associated with the same effect: an increased rate of survival. Furthermore, their effects are additive (ie, noninteracting). Finally, our findings revealed a dose-effect correlation between the time the causative drug was stopped and the risk of dying (ie, the later the causative drug was stopped the higher the mortality rate). We did not detect a dose-effect relationship for drug elimination half-lives. This may be owing to the confounding effect of the suboptimal measure of drug withdrawal time (we measured drug administration timing in days and drug elimination half-life in hours). Changes in the hour when the last dose of a drug was administered cannot be accounted for and may mask the effect of variations in drug half-life. Our inability to estimate the risk of 1 hour of half-life in contrast with the increased risk associated with long half-lives in a dichotomous analysis may also be related to the fact that the distribution of mean half-lives is skewed. Using the mean half-lives of drugs as indicated by textbooks instead of the actual half-lives in individual patients is a source of error that may explain the discrepancy between the findings of a continuous and a dichotomous analysis.

The mechanisms that can explain increased mortality following longer presence of a causative drug in the body once a drug reaction has started are unknown. Most of the complications of TEN or SJS are considered to be the result of the loss of skin functions. As such, they are supposed to be proportional to the extent of epidermal destruction, as is the case with patients with burns or other diseases resulting in acute skin failure.[4] However, the prognosis appears to be more severe in patients with TEN than for those with second-degree burns involving the same surface[10,17]; our data showed that the 4 groups we examined had a different prognosis in spite of a similar extent of epidermal detachment. Extracutaneous effects of TEN probably account for those differences in prognosis, as previously suggested.[4,17] Future studies should include systemic findings to obtain estimates of prognosis.

Our findings were obtained in a series of patients with SJS or TEN. We have no data to suggest that early withdrawal of the causative drug(s) may have a similar effect on the prognosis of other types of severe adverse drug reactions. With regard to common maculopapular rashes, we believe that our findings are relevant only for rare cases with mucous membrane symptoms or signs that may indicate a risk of progression to TEN or SJS.

There are some limitations of our study. First, our method was not experimental but observational, implying that causation can be proposed but not firmly established. However, since it would be unethical to perform a randomized controlled trial of the effect of prolonging drug administration, our findings are based on the best data currently available. Second, since our study was retrospective, data quality and patient selection could be matters for concern. However, the validity of our data is supported by the use of a standardized questionnaire. The