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CLINICAL REPORT

Dexamethasone Pulse Therapy for Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis

Sylvia H. KARDAUN and Marcel F. JONKMAN
Center for Blistering Diseases, Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Mortality in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is high. Apart from intensive supportive therapy, no generally accepted specific treatment regimen exists. The role of corticosteroids in SJS/TEN is controversial. It is possible that high-dose pulse therapy with corticosteroids might be an improvement on long-term lower dose therapy, by combining higher efficacy with a diminished risk both of infection and of delayed wound healing. The aim of this study was to evaluate the efficacy of dexamethasone pulse therapy with respect to mortality and healing time of patients with SJS/TEN. A small, uncontrolled series of consecutive inpatients with SJS/TEN was treated with dexamethasone pulse therapy. The efficacy of this treatment was assessed retrospectively using SCORTEN. Twelve patients were included over a period of 10 years. One patient died, while SCORTEN predicted a fatal outcome of 4 patients. Stabilization was reached after 2.3 days on average, total re-epithelialization after 13.9 days. The results of this study bear no statistical relevance due to the small number of patients. In conclusion, short-term dexamethasone pulse therapy, given at an early stage of the disease, may contribute to a reduced mortality rate in SJS/TEN without increasing healing time. A larger controlled trial is warranted to investigate further the use of dexamethasone pulse therapy in SJS/TEN. ***Key words: toxic epidermal necrolysis; Stevens-Johnson syndrome; dexamethasone; pulse therapy.***

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Sylvia H. Kardaun, MD, Center for Blistering Diseases, Department of Dermatology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, NL-9713 GZ Groningen, The Netherlands. E-mail: s.h.kardaun@derm.umcg.nl

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but serious mucocutaneous reactions with extensive epithelial sloughing and systemic symptoms, most often caused by drugs (1). More than 100 drugs have been associated with SJS/TEN, most often implicated are anti-epileptics, sulphonamides, β-lactam antibiotics, non-steroidal anti-inflammatory drugs and allopurinol. SJS and TEN are part of a spectrum, which is artificially divided into 3 groups: SJS when the total detached and detachable body surface area (TBSA) is less then 10%, TEN when it is over 30%, and SJS/TEN-overlap when it is between 10% and 30% (2). The incidence of SJS is 1.2–6 per million per year and that of TEN 0.4–1.2 per million per year (1). Mortality rates reported in the literature vary due to differences in the definition of SJS and TEN, in populations and in treatment, but they are generally high. In adults mortality due to TEN is most often cited as 30–50% (1, 3–5). Sepsis and multi-organ failure are the main causes of death. Recovery is usually slow and may take 3–6 weeks (1). As a rule skin lesions heal without scarring, whereas mucosal scarring and strictures are frequent late complications. Late eye complications, potentially leading to blindness, occur in up to 50% of cases (6).

Apart from intensive supportive therapy, a generally accepted regimen for specific treatment of SJS/TEN is lacking. Treatment options include systemic corticosteroids, intravenous immunoglobulin therapy (IVIG), other immunosuppressive therapy, or no systemic treatment. Historically high-dose corticosteroids were advocated, but since the mid-1980s the use of corticosteroids in SJS/TEN has been controversial and is even considered detrimental by some authors (1, 7–9).

Intravenous (i.v.) pulse therapy with corticosteroids is used in severe, often autoimmune, diseases, as it is assumed to share high efficacy with fewer side-effects than long-term lower dose corticosteroids. It has been used in dermatology since 1982 for several dermatological diseases that are often refractory to standard therapy, such as pyoderma gangrenosum and pemphigus (10). Although we demonstrated recently that there was no benefit of giving long-term adjuvant oral corticosteroid pulse therapy in addition to conventional treatment in patients with pemphigus vulgaris, the hypothesis that i.v. corticosteroid pulse therapy could be useful in TEN is still valid, since the pathomechanism of both diseases is different, and corticosteroid pulse therapy is applied as short-term monotreatment in TEN (11). There are only a few case reports describing pulse therapy in TEN (12, 13). Initially, 1000 mg methylprednisolone was usually used, but recently dexamethasone has often been chosen for pulse therapy because it combines a strong immunosuppressive glucocorticoid with a negligible mineralo-

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corticoid effect. We studied the effect of dexamethasone pulse therapy (DPT) in 12 patients with SJS/TEN.

METHODS

From 1993 to 2003, we treated 12 consecutive patients who were referred to our department with SJS/TEN, using a standardized care protocol that did not require ethics review from our institution. All data were analysed retrospectively.

After anamnesis and physical examination, diagnosis was verified by histopathology of direct fresh-frozen sections of the skin, enabling quick diagnosis and differentiation from other diseases, especially staphylococcal scalded skin syndrome. Diagnosis was subsequently confirmed by routine histopathology, while immunofluorescence analysis of the skin and serum was performed in order to exclude immuno-bullous diseases. The date of onset of disease was determined from the patient's medical history. Assessment of drug culpability (i.e. the empirical risk of a drug and the time-relation between drug use and the adverse reaction) was also based on the patient's history. All suspected and non-essential drugs were stopped. Demographic and specific disease data are presented in Table I.

Specific systemic therapy was started as soon as the diagnosis was established. In the first 4 patients we combined i.v. dexamethasone 100 mg, given within 30–60 min on 3 consecutive days, with one dose of cyclophosphamide 500 mg on the first day, analogous to the pulse for pemphigus vulgaris used by Pasricha (14). After the fourth patient, cyclophosphamide was omitted and the regimen changed to i.v. dexamethasone 1.5 mg/kg body-weight as pulse therapy for 3 consecutive days.

The patients were seen by a multidisciplinary team and received intensive supportive care according to a standard protocol. This included early fluid and electrolyte replacement, aggressive nutritional supplementation, and monitoring of vital functions. An ophthalmologist was routinely consulted about daily eye care. Meticulous wound care included lubricants, topical antibiotics and non-adhesive silicone wound dressings. Nursing was barrier protected and the patients were treated on an air-fluidized bed in a specialized humidity- and temperature-controlled unit with, for aseptic reasons, a laminar down-flow stream. Epidermal involvement and TBSA were charted daily to determine the date of arrest of progression and of complete re-epithelialization (Table II). Additional investigations, including haemograms, biochemical tests, urine analysis, coagulation tests, fluid balance, body weight and bacteriological analysis, were performed on a regular basis. The use of lines and catheters was avoided as much as possible, and the venous line was maintained as short as possible. H2-blocking agents were administered in case of a history of gastric upset. To prevent intestinal Candida overgrowth we supplied oral nystatin, and for thrombosis prophylaxis nadroparin was given subcutaneously. Pain killers and sedatives were provided as needed. Antibiotic prophylaxis was not given, but antibiotics were supplied immediately when clinically warranted. After discharge, a follow-up of 8±2 weeks was performed, and in cases where late sequelae were observed, also 2 years later.

SCORTEN, a validated TEN-specific severity-of-illness-score, ranking severity and predicting mortality, was calculated retrospectively to assess the efficacy of DPT. SCORTEN is based on 7 independent risk factors (age, heart rate, malignancy, TBSA, and serum urea, bicarbonate and glucose levels). The predicted mortality progressively depends on the number of factors present (15).

Table I. *Clinical characteristics of patients with toxic epidermal necrolyis (TEN) or Stevens-Johnson syndrome (SJS)*

Pat. no.	Age (years)/ Sex	TBSA on admission	TBSA max.	No. of mucosal sites involved	Diagnosis	SCORTEN on admission
1	71/M	26	32	5	TEN	4
2	33/M	45	62	4	TEN	2
3	44/F	30	72	5	TEN	2
4	15/M	3	9	3	SJS	0
5	62/F	60	70	3	TEN	3[a]
6	70/F	18	19	3	SJS/TEN	3
7	78/M	23	41	2	TEN	5[a]
8	53/F	53	61	4	TEN	3
9	58/F	11	20	2	SJS/TEN	3[b]
10	77/M	6	19	2	SJS/TEN	3
11	84/F	20	29	2	SJS/TEN	3
12	22/M	25	48	2	TEN	2[c]
Mean	55.6	26.7	40.2	3.1		2.8

[a]Brain tumour/metastasis.
[b]Systemic lupus erythematosus (SLE).
[c]Bone marrow transplant for haematological malignancy.
TBSA, total detached and detachable body surface area, %.

RESULTS

Twelve consecutive patients (6 males, 6 females) were treated. Their mean age was 55.6 years (age range 15–84 years). TBSA and characteristic cutaneous findings led to the classification of 1 SJS, 4 SJS/TEN-overlap and 7 TEN. In all patients, 2 or more mucosae were affected. The mean SCORTEN on admission was 2.8 (range 0–5) and predicted a mortality of 4 cases (25%). The mean delay between occurrence of first blister and first DPT was 2.8 days (range 1–6 days). Disease stabilization was achieved after a mean of 2.3 days (range 1–5 days) after DPT. The mean time of healing (not stabilization) was strongly influenced by patient 1, who had extensive pre-existing burn scars. When we exclude these data, healing time from first DPT was 13.9 days (range 8–24 days), while from first blister it was 16.8 days (range 10–30 days).

Patient 7 died; according to the consulting neurologist the cause of death was brain oedema due to metastasis, while his skin had practically healed. All other patients survived without major sequelae. Sepsis was found in patients 1 and 2, and suspected in patient 5. In addition, patients 1 and 5 had serologically proven herpes simplex virus (HSV) type 1 infection while leukopaenia was present, probably contributing to protracted healing. In patient 1 neutropaenia ($0.04\times10^3/\mu l$) accompanied severe leukopaenia ($0.4\times10^3/\mu l$). In patients 2 and 3 the respiratory tract was involved, leading to respiratory insufficiency; patient 3 needed mechanical ventilation. Though all patients experienced eye involvement in the acute phase, late sequelae were relatively mild and severe impaired vision was not encountered. Patients 2 and 8 developed mild trichiasis, while patients 2 and 12 were left with dry eyes. Five patients (nos 2, 3, 4, 8 and 12) experienced hyper- and/or hypo-pigmentation of the skin,

Table II. Suspected drugs and course of the disease (in days) before and after dexamethasone pulse therapy (DPT)

Patient no.	Suspected drug	Lag time[a]	Blister to DPT	DPT to stabilization	DPT to healing	Blister to healing	Remarks
1[b]	Sulphamethoxazole + trimethoprim	2[c]	1	2	72	73	Burn scars, HSV
2[b]	Acetylsalicylic acid	<14	3	2	15	18	
3[b]	Carbamazepine	12	1	2	17	18	
4[b]	Carbamazepine	14	2	2	8	10	
5	Phenytoin	36[d]	6	2	24	30	Late referral, HSV
6	Allopurinol	5	4	1	14	18	
7	Phenytoin	37[d]	1	3	9	10	
8	Carbamazepine	17	2	2	17	19	
9	Omeprazole	29[d]	4	3	14	18	
10	Amoxicillin + clavulanic acid	4	3	5	14	17	
11	Terbinafine	19	2	1	12	14	
12	Sulphamethoxazole + trimethoprim	10	4	3	9	13	
Mean 1–12			2.8	2.3	18.8	21.5	Overall
Mean 2–12			2.9	2.4	13.9	16.8	Excluding case 1

[a]Lag time: time between first drug administration and first blister.
[b]Also received cyclophosphamide 500 mg on day 1.
[c]Eight years earlier: toxic epidermal necrolysis after sulphamethoxazole + trimethoprim.
[d]Chronic corticosteroid use: daily dose equivalent to 15–30 mg prednisolone.
HSV: herpes simplex virus.

most often transient. Hypohidrosis and dystrophic nails were observed in patient 8. Apart from slight transient glycaemia in some patients that might have been caused by dexamethasone, we did not observe any side-effects of dexamethasone.

DISCUSSION

The pathophysiology of SJS/TEN is not yet fully elucidated, although significant progress has been made. Massive accelerated apoptosis has been proposed as the main mechanism underlying keratinocytic death in SJS/TEN. Several pathways can lead to apoptosis. CD8-positive T cells and macrophages play an important role in the extensive epithelial necrosis and subepithelial detachment (16). Various (pro)inflammatory cytokines including tumour necrosis factor (TNF)-α may contribute to epidermal cell death, as well as to fever and malaise. It has been suggested that, in SJS/TEN, apoptosis is mediated principally through activation of the Fas receptor by increased Fas ligand expression, but others have suggested that it is mediated mainly by TNF-α, perforin and granzyme B. Interferon-γ upregulation of keratinocytes also plays a role (17–19).

In SJS/TEN the barrier function of the skin is lost due to full-thickness epithelial necrosis. Hence, disturbance of fluid, protein, and electrolyte balance leading to hypovolaemic shock and local and systemic infection with the threatening of sepsis, often leading to multiorgan failure, are the most important causes of death. The main point in dealing with SJS/TEN patients is to restore the barrier function of the skin and mucosae as quickly as possible and in the meantime prevent the effects of this barrier loss.

Knowledge of the treatment of SJS/TEN rests greatly on anecdotal observations, empirical experience and retrospective studies. Apart from direct withdrawal of the culprit drug and supportive care, there are no generally accepted guidelines for the specific treatment of SJS/TEN, and few controlled clinical trials have been performed due to the rarity and severity of the disease (5, 19). Several specific treatment options have been proposed on theoretical grounds. Some with promising results and others, e.g. thalidomide, with increased mortality, possibly due to paradoxically enhanced TNF-α production (4, 19). The supposed rationale for IVIG is its capacity to inhibit activation of the death receptor by Fas-blocking antibodies, but its clinical results were contradictory (3, 5, 17, 20, 21). The use of corticosteroids in SJS/TEN is controversial (7–10, 22, 23). The precise action of corticosteroids in inflammatory diseases is still not well understood. They have pleomorphic immune-modulating effects, e.g. through inhibition of numerous cytokines (10). Nowadays the use of corticosteroids in SJS/TEN is generally not advocated because of the possibility of delayed healing and the risk of infection (7, 9, 23). However, this opinion is based on only a few case series. Moreover, some cases in which it was stated that a better outcome was related to avoidance of corticosteroids had in fact taken corticosteroids for a mean of 3.5 days prior to referral. The general negative opinion of corticosteroids is probably because they are often given too late, in too low a dose, and for too long during the process. During the healing phase corticosteroids may indeed impair wound healing and promote sepsis. However, short courses of high-dose corticosteroids in early SJS/TEN have a good rationale, as immune mechanisms are directly responsible for the cascade of events leading to apoptosis. Hence, we

challenged the general opinion of corticosteroids being detrimental in the treatment of SJS/TEN.

Dexamethasone is a potent glucocorticoid (about 7 times as potent as the same dose of prednisolone) with a continuous action level, due to its relative long biological half-life (36–54 h). It has pleomorphic effects on the immune system and may inhibit epidermal apoptosis by several mechanisms: inhibition of T-cell activated apoptosis by suppression of various cytokines such as TNF-α; inhibition of interferon-γ induced apoptosis; and inhibition of Fas-mediated keratinocyte apoptosis (10, 24).

We gave DPT 1.5 mg/kg i.v. in 30–60 min on 3 consecutive days, thus avoiding long-term use of corticosteroids. Cyclophosphamide, added in the pemphigus regimen to prevent relapses, was omitted after patient 4 (see table II), as relapses are not to be expected after withdrawal of the culprit drug. We saw no significant change in outcome and healing time.

Patients 5 and 7 had metastatic brain tumours, and patient 9 had systemic lupus erythematosus, for which they chronically received corticosteroids. These patients developed the SJS/TEN reaction after a longer lag time (time between first drug administration and first blister). This phenomenon has been described previously (22); however, in patients 5 and 7 it might also be attributed to the culprit drug phenytoin, known for its potentially long lag time. Leukopaenia, regularly encountered in TEN, occurred in patients 5 and 1, in the latter neutropaenia was also present. Both patients experienced sepsis and HSV infection, probably attributing to delayed wound healing.

The efficacy of DPT was evaluated according to arrest of further epidermal or mucosal detachment, healing time in days, outcome and sequelae. The patients stabilized after an average of 2.3 days, while total re-epithelialization was reached after 13.9 days. Despite SCORTEN predicting a mortality of 4 patients, only one died. Serious late sequelae of the mucosae, especially of the eyes were not found.

Comparison with published results is difficult. Most records of therapeutic trials in TEN are case series without controls. We calculated SCORTEN as validated predictive score for the outcome in SJS/TEN.

In a large, multi-centre, epidemiological study the average period for stabilization was 4 days for SJS and 5.8 days for TEN. Healing was almost complete 20–30 days after hospitalization (25). In another study, therapy with IVIG was started 4.1 days after the start of the disease and healing was complete 18 days after admission. SCORTEN predicted 8.2 deaths, while 11 actually occurred (3). The authors concluded IVIG could not be recommended as a standard treatment for SJS/TEN. On the other hand, several IVIG studies mention surprisingly short periods of stabilization and/or healing (20, 21). In interpreting these results, one should also consider the time-lapse before treatment is started, as without treatment the period of progression may last 7–10 days (19, 25). Starting treatment late in the process implies that it is difficult to measure the effect of treatment on stabilization. Since we started quite early, we believe from our data that DPT did result in a relatively quick stabilization and healing and suggest that DPT may even have halted the process of apoptosis.

Although the results of this study bear no statistical relevance due to the small number of patients, we conclude that short-term DPT, given at an early stage of the disease, may contribute to a reduced mortality rate in SJS/TEN without increasing healing time. A larger controlled trial is warranted in order to investigate further the use of DPT in SJS/TEN.

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