Intensive Care Med (1999) 25: 1307–1310

BRIEF REPORT

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Lack of significant treatment effect of plasma exchange in the treatment of drug-induced toxic epidermal necrolysis?

Received: 4 May 1999
Final revision received: 26 August 1999
Accepted: 1 September 1999

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Abstract *Objective:* Comparison of outcome in patients with toxic epidermal necrolysis (TEN) in patients who received plasma exchange (PE) compared with the results in two other centres that used almost identical treatment protocols but without PE.
Design: Retrospective comparative case series with two recently published case series serving as controls.
Setting: National burns intensive care unit (ICU) and Department of Transfusion Medicine at Linköping University Hospital, Sweden.
Patients: 8 consecutive patients admitted with TEN who received PE during 1987–1997.
Interventions: Neither prophylactic antibiotics nor cortisone were used. The patients were given a median of 5.5 PE treatments (range 1–8).
Results: Eight patients with a median (range) age of 45 years (5–89) and with a median skin involvement total body surface area (TBSA) of 38 % (12–100) were treated. The length of stay in the burns ICU was 15 (13–25) days and the time from onset of the cutaneous signs until complete re-epithelialisation was 24 days (13–55) for the seven survivors. Five patients fulfilled the diagnostic criteria of sepsis. One patient with extensive ischaemic cardiac disease developed septic shock and died (mortality 12.5 %). Two patients developed side effects from PE.
Conclusions: To our knowledge, this is the largest series yet presented using PE in the treatment of TEN. Our results, in patients with less cutaneous involvement, similar causative agents, and similar demographic data as in the other two studies (controls), were no different as far as mortality, length of stay, or time to re-epithelialisation were concerned. This finding does not support the use of PE in the treatment of TEN.

Key words Antibiotics – Cortisone – Lyell – Plasma exchange – Therapeutic plasmapheresis – Toxic epidermal necrolysis – TEN

Introduction

Toxic epidermal necrolysis (TEN) is a rare but life-threatening disorder with an incidence of about 1 per million [1]. It is generally suggested that these patients are best cared for in specialized burns intensive care units (ICU), as they are in Sweden. The Linköping Burns ICU, as one of two designated national burns ICUs, receives about one to three patients a year given the catchment area and a similar incidence of TEN in Sweden as in the United States. Three aspects of the treatment of TEN have been debated over the years: the use of prophylactic antibiotics [2], corticosteroids [2,3], and plasma exchange (PE) [1,4,5].

At the beginning of the 1980s, PE was given as treatment for TEN for the first time and good results were claimed. One patient in France and five in Germany all improved rapidly [4,6]. The speculation from these re-

Table 1 Patient data and treatment outcome (*MOF* multiple organ failure)

Age/sex	TBSA (%)	Causative agents	Days before arrival at ICU	No of PE treatments	Complications	ICU stay (days)	Time from onset to complete re-epithelialisation (days)	Outcome
21 M	40	Chlormezanone	4	5	Allergic reaction	14	38	Lived
47 F	100	Dextropropoxyphene, phenazone, codeine, thioridazine	36	2	Sepsis	20	55	Lived
43 M	60	Chlormezanone	3	8	Sepsis	24	17	Lived
5 M	35	Penicillin	2	7	Sepsis	13	13	Lived
67 F	46	Clindamycin	8	4	Septic shock, MOF	5	–	Died
69 F	36	Flucloxacillin	1	7	Sepsis	25	25	Lived
38 F	30	Ketoprofen-gel	9	6	–	15	24	Lived
89 F	12	Trimethoprim-sulfamethoxazole	1	1	Hypotension	15	16	Lived

sults was that plasmapheresis filters out toxic metabolites and immunological factors involved in the disease [6]. Since 1987, PE has become the regular treatment of patients with TEN at the University Hospital, Linköping, Sweden. The aim of this retrospective comparative case series was to evaluate the effect of this treatment.

Materials and methods

We have examined the records of all patients admitted to the burns ICU with the diagnosis of TEN. From 1987 to 1997 all such patients were given PE.

As we do not have a control group ourselves (not treated with PE), we have chosen to compare our results with two recently published studies in which PE was not used but in which other aspects the treatment protocols were similar [7,8].

If corticosteroid treatment had been started before arrival it was discontinued. Antibiotics were not given prophylactically. All patients had their wounds revised and dressings changed daily under general anaesthesia. The wounds were covered with paraffin gauge (Jelonet).

PE was performed by intermittent flow centrifugation (using Haemonetics model 30 cell separator; two patients) or by continuous flow centrifugation (Cobe Spectra cell separator; six patients). PE was started on the day of arrival at the unit (five patients) or 1–3 days after arrival (three patients). The patients were given a median of six (one to eight) PEs at an interval of 1–3 days. Approximately one plasma volume was exchanged each time and was replaced by plasma (6 treatments) or albumin (34 treatments).

Results

Between 1987 and 1997 a total of eight patients were treated for TEN and all were given PE. Their median age (range) was 45 years (5–89) and the median (range) total body surface area (TBSA) affected was 38% (12–100). It was, however, not specified how extensive the area of detachment was. The median number of days before arrival at the burns ICU after the first symptoms was 3.5 days (1–36) (Table 1).

The median number of PE treatments given was six (one to eight), with no complications except in two cases – in one an allergic reaction (urticaria) against plasma and in the other transient hypotension with dyspnoea. Five patients developed severe sepsis and one with extensive ischaemic cardiac disease died in septic shock with multiple organ failure. The median length of stay in the burns ICU was 15 days (13–25) and the median time from onset of the cutaneous manifestations until complete re-epithelialisation was 24 days (13–55) in the survivors (Table 1).

Discussion

TEN is the most severe cutaneous drug reaction. It starts with erythema and influenza-like symptoms and progresses quickly to a bullous epidermal full-thickness necrosis and detachment resembling a second degree burn. Mucous membranes are often involved. Erythema exudativum multiforme major and Stevens-Johnson syndrom (SJS) are closely related, and there are no widely accepted clinical criteria to separate these three diseases [9]. A classification has been proposed by which the diagnosis is primarily based on the extent of detached epidermis at the worst stage of the disease, because detachment is a major prognostic factor [10]. TEN is diagnosed if the epidermal detachment is more than 30% of TBSA and SJS if the epidermal attachment is less than 10%. This is in accordance with the original publications by Lyell (1956) and Stevens and Johnson (1922). For patients with areas of epidermal detachment

Table 2 Comparisons between our study and two recently published ones [7, 8]

	No. of patients	Mean (range) age (years)	Mean (range) TBSA (%)	Plasma exchange	Mean (range) time from onset to complete re-epithelialisation (days)	Mortality [No. (%)]
Our study	8	47 (5–89)	45 (12–100)	Yes	27 (13–38)	1/8 (12.5)
Koo and Foo [7]	22	44 (7–60)	57 (30–90)	No	20 (7–53)	2/22 (9)
Yarbrough [8]	14	47 (16–77)	78 (45–100)	No	16 (Not stated)	2/14 (14)

of between 10 and 30 %, the category overlap TEN–SJS is proposed. Using these criteria for the diagnosis TEN, it seems reasonable to think that our patients as well as those in the control studies were correctly diagnosed as having TEN. However, there was one patient in our study who fell somewhat short of the 30 % TBSA criterion.

The treatment of TEN apart from the three aspects that are debatable (prophylactic antibiotics, corticosteroids, and PE) is mainly supportive and may not be thought to vary much between centres. The cases of the eight patients in our study were collected over 10 years, which is a confounding factor as the general treatment of burns may be claimed to have improved substantially over this period. The change in the exchange fluids in the PE from plasma to albumin that has occurred over time may also have affected the results.

TEN is caused by drugs in almost all cases. When comparing our study and the two control studies, it seems reasonable to state that the causative agents are as expected and it suggests that the three studies are also comparable in this respect. The pathogenesis of TEN is unknown, but some patients with TEN metabolise the offending drug in an unusual way, which leads to increased production of reactive metabolites [11]. It has also been suggested that reactive metabolites behave as haptens, adhere to carrier protein on the membrane of epidermal cells, and induce an immune response. These theories are the foundation for the pathogenesis of PE. An increase of macrophages and CD8 T-lymphocytes has been found, and these may act as cytotoxic effector cells. Autoantibodies have not been found [1].

The mortality varies greatly in different studies – between 10 and 70 % with a mean of about 29 %. At least half of these deaths are the result of sepsis [2]. Factors associated with a bad prognosis are allergy, old age, large percentage of denuded skin, delayed transfer to burns ICU, and continued steroid treatment after skin loss has started [3,5]. Given the mortality in the three studies presented, we suggest that the mortality of TEN is declining, but the reason for this is not clear. Possibly it is for the same reasons that explain the improvement in conventional burn care.

In summary, we found two recent studies with which to compare our results. The treatment protocol of our study was similar to theirs except that PE was not used in their case. Both the length of stay in the burns ICU and the time until complete re-epithelialisation were longer in our study (Table 2). Mortality did not differ between these three studies. The TBSA % involvement was less in our study, but this measurement is somewhat unreliable and is often overestimated by physicians [9]. PE is a treatment with few complications but it is expensive. Thus, we were unable to find any aspect that turned out better in our group of patients than in those who did not receive PE. This finding does not support the use of PE in the treatment of TEN.

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