Evaluation of the Treatment of Toxic Epidermal Necrolysis during a Ten-year Period, from 1982 to 1991, with Corticosteroids as the Main Therapy

Dr. Adhi Djuanda, dr

Abstrak

Pengobatan nekrolisis epidermal toksik (NET) dengan atau tanpa kortikosteroid masih kontroversial. Pada penelitian ini dilakukan penilaian pengobatan NET dengan obat utama kortikosteroid selama 10 tahun (1982-1991). Obat yang terutama ialah deksametason dengan dosis 20-30 mg sehari, i.v. Di samping itu penderita juga mendapat antibiotik, ACTH, dan obat anabolik. Jika tidak tampak perbaikan setelah beberapa hari ditambahkan transfusi darah 300 cc dua hari berturut-turut. Juga diatur pemberian cairan dan keseimbangan elektrolit. Selama 10 tahun terdapat 33 kasus terdiri dari 11 pria dan 22 wanita, berumur antara 8-60 tahun. Sebagai kemungkinan penyebabnya, 1 kasus karena ikan, 3 kasus karena infeksi, 6 kasus tidak diketahui penyebabnya, sedangkan sisanya (23 kasus) karena alergi obat. Tujuh penderita meninggal (21,2 %) umumnya karena bronkopneumonia dan sepsis. Angka mortalitas tersebut lebih rendah daripada pengobatan NET tanpa kortikosteroid seperti yang disebut dalam kepustakaan (48,6 %).

Abstract

The therapy of Toxic Epidermal Necrolysis (TEN) with or without corticosteroid is still controversial. In this study an evaluation of the treatment of TEN with corticosteroid as the main therapy, during a ten year period, from 1982 to 1991, is performed. The main therapy was dexamethasone 20-30 mg daily, i.v. Besides that the patients also received antibiotic, ACTH and anabolic agent. If there was no improvement after several days, 300 cc blood transfusion for 2 successive days were added. The fluid and electrolyte balance were regulated. During the ten year period there were 33 cases, consisting of 11 males and 22 females, their age varied between 8-60 years. The probable causes of the disease were, 1 case due to fish, 3 cases due to infections, 6 cases unknown, and the rest (23 cases) probably were due to drug allergy. Seven patients died (21.2 %), mostly due to bronchopneumonia and sepsis. This mortality rate is lower than the therapy of TEN without corticosteroid as mentioned in the literature (48.6 %).

***Keywords** : Toxic Epidermal Necrolysis, Corticosteroid, Mortality rate*

INTRODUCTION

Toxic Epidermal Necrolysis (TEN) was first mentioned by Lyell in 1956. He reported 4 patients suffering from a disorder, which he considered as probably caused by drug therapy, staphylococcal infection and idiopathic conditions.[1]

Although thereafter many cases of TEN has been recorded, the pathogenesis is not yet clear. By some it is regarded as a severe form of Stevens-Johnson's syndrome, because both disorders may occur as adverse drug reactions to a similar spectrum of drugs. Others are of the opinion that there is no correlation whatsoever between both entities as each present a quite different histological picture.[2]

In accordance with these different views on the pathogenesis of TEN several modes of treatment has been advocated. Not a few clinicians recommend the use of corticosteroids with or without antibiotics.[3] Others do without corticosteroids just maintaining the fluid and mineral balance.[4] Some favour treating them as secondary burn.[5] Kananbroo et al. treated TEN as a severe drug induced reaction, using plasmaphoresis.[6]

The purpose of this paper is to evaluate the therapy of TEN based on corticosteroids as the principal therapeutic agent.

Department of Dermatology and Venereology, Faculty of Medicine University of Indonesia, Jakarta, Indonesia

MATERIALS AND METHODS

Records of all patients with TEN admitted to our department during 10 years from January 1982 to December 1991 were analyzed.

The diagnosis of TEN was based on the anamnesis and clinical picture : prodromal symptoms precursive to an abrupt onset, usually with fever and a bad general condition, and leucocytosis. The main lesion consisted of epidermolysis, accompanied by erythema, vesicles, bullae and some with purpura. The mucous membrane of the body orifices, such as the mouth and the external urethral orifice, may be involved, and the eyes also, resulting in conjunctivitis.

The instituted therapy was mainly corticosteroids. Dexamethasone was administered by intravenous route, the dose varying from 20- 30 mg/day according to the severity of the disease. After improvement the dose of dexamethasone was quickly tapered off. After the patient was able to swallow and the daily dose of dexamethasone was reduced to 10 mg, a switch-over to 30 mg prednisone tablets was given. Each day thereafter the dose was further reduced to 10 mg per day; and then withdrawn.

Corticosteroids therapy was combined with an antibiotic, usually gentamycin 2 x 60 mg or 2 x 80 mg daily.

If this regimen did not result in any notable improvement within a few days, blood transfusion was added, 300 cc daily for 2 successive days. In these cases, and when patients were unable to take food or fluid, special attention were paid to fluid intake. Fluid being replenished by way of infusion of Darrow-glucose and 5% glucose solution.

Haemostatic drugs were especially indicated in cases accompanied by a widespread purpura. An anabolic agent was given to neutralize the catabolic effect of corticosteroids. Decrease of potassium ion due to corticosteroids was countered by the administration of KCl given as kalium durules with a dose of 3 x 500 mg daily.

RESULTS

Thirty three cases of TEN were admitted in our department during a period of 10 years between 1982-1991. The cases consisted of 11 males and 22 females, varying in age between 8-60 years (see table 1). As probable cause were noted : 1 case was due to fish, 3 cases were due to infections (1 case due to *Pseudomonas aeruginosa,* 1 case due to *Pseudomonas mirabilis,* and the other was unknown), 6 cases were unknown, and the rest (23 cases) probably were due to drug allergy (see table 2).

As the most probable cause of drug allergies were analgetics and antipyretics (paracetamol, metapiron and mefenamic acid) in 8 cases, followed by tetracycline in 3 cases; anticonvulsant (carbamazepine) and allopurinol respectively in 2 cases; sulfonamide and its derivate (dapsone) in 2 cases; ergometrine maleat, amoxycillin, cefradocyl monohydrate, H1 blocking agent (dimenhydrinate), a sedative (chlordiazepoxide) and herbs respectively in 1 case.

Duration of treatment lasted from 2-3 weeks. Of the 33 cases, 7 (21.2 %) ended fatally, mostly due to bronchopneumonia and sepsis, while in other cases a complete cure were obtained.

Table 2. Drugs which probably cause TEN and the number of cases

Number	Drug	Number of case
1	Paracetamol	6
2	Tetracycline	3
3	Carbamazepine	2
4	Allopurinol	2
5	Metapiron	1
6	Mefenamic acid	1
7	Sulfonamide	1
8	Dapsone	1
9	Amoxycillin	1
10	Ergometrin maleate	1
11	Cefadroxyl monohydrate	1
12	Dimenhydrinate	1
13	Chlordiazepoxide	1
14	Herbs	1

DISCUSSION

Until recently there is still no agreement regarding the diagnostic criteria of TEN. Ruiz Maldorado suggested the introduction of a new terminology for TEN, being acute disseminated epidermal necrolysis (ADEN). He distinguished three types : type 1 replacing drug associated Stevens-Johnson syndrome, type 3 replacing drug associated Lyell syndrome and type 2 for transitional cases.[4]

Revus et al. are of the opinion that patients should be considered to have TEN rather than Stevens-Johnson syndrome, if the confluence of the cutaneous lesions led to a large plaque of necrolysis, uncovering the dermis in an area of at least 10% of the body surface.[1] This criteria is not quite justified, because at the onset of TEN the epidermolysis is localized, expanding later on, finally becoming generalized.

Golstein et al.[2] mentioned other diagnostic criteria, widespread blisters with a morbilliform or

Table 1. Clinical data in 33 patients with toxic epidermal necrolysis during 10 years (1982-1991)

Patient/ Sex/Age,	Year of admision	Probable cause	Result of therapy	Cause of death
1/F/19	1982	sulfonamide	cured	
2/M/18	1982	herbs	died	broncho-pneumonia
3/F/16	1982	amoxycillin	cured	
4/M/25	1982	methylergometrine	died	sepsis
5/M/53	1984	paracetamol	cured	
6/M/11	1984	*Pseudomonas aeroginosa*	cured	
7/M/37	1985	cefadroxil monohydrate	cured	
8/M/8	1986	carbamazepine	cured	
9/F/19	1986	tetracycline	died	broncho-pneumonia + sepsis
10/F/30	1986	ampicillin	cured	
11/F/30	1986	dimenhydrinate	cured	
12/F/32	1986	chlordiazepoxide	cured	
13/M/29	1986	tetracycline	cured	
14/F/30	1986	dapsone	cured	
15/F/28	1987	tetracycline	cured	
16/F/22	1988	infection	cured	
17/F/40	1989	unknown	cured	
18/F/17	1989	paracetamol	cured	
19/F/23	1989	paracetamol	cured	
20/F/50	1989	paracetamol	died	renal-failure
21/M/26	1989	allopurinol	cured	
22/M/60	1989	metapiron	cured	
23/F/24	1989	*P. mirabilis*	cured	
24/F/39	1989	unknown	died	pulmonary edema, sepsis
25/F/50	1989	unknown	cured	
26/F/24	1989	unknown	died	broncho-pneumonia
27/F/36	1989	allopurinol	cured	
28/F/24	1990	paracetamol	cured	
29/M/33	1990	unknown	died	broncho-pneumonia
30/F/27	1990	seafood	cured	
31/M/38	1990	paracetamol	cured	
32/F/20	1990	carbamazepine	cured	
33/F/40	1991	unknown	cured	

confluent erythema and associated skin tenderness, the absence of target lesions, sudden onset and generalization within 24-48 hours, the histopathologic picture showing a confluent fullthickness epidermal keratinocyte necrosis, leaving the cytoplasma of keratinocytes eosinophilic and glossy, and a minimal to absence of dermal infiltrate.

The diagnosis of TEN in this study was based on clinical picture as mentioned above. The main lesion being generalized epidermolysis.

As is the matter with the diagnostic criteria of TEN, no agreement has been reached concerning its treatment. Until recently, no specific treatment is known, and actually not one mode of therapy can be considered superior. In fact the treatment of TEN with corticosteroids is according to several sources of literature still controversial.[3,7]

In 1973, Bjornberg reported 15 cases of TEN in which high dosages of steroids immediately stopped the progression of the disease, 11 patients treated with steroids in combination with antibiotics survived, 2 of 3 patients who received steroids alone died from infections.[3]

Some clinicians recommend the early administration of high dosages of steroids, ranging from 100 mg to 200 mg prednisone or equivalent of other corticosteroids.[7] Fritch and Elias used the equivalent of 150 to 250 mg prednisone per day. This dosage should be

maintained until progression of the skin lesions is halted and should then be tapered off very cautiously.[3]

The reason for treating TEN with corticosteroids in our department is, that in our view TEN should be regarded as allergic reactions. In severe cases dexamethasone with a dose of 20 to 30 mg daily were used, this being aequivalent to 133-200 mg prednisone. This dose is almost in accordance to that suggested by Fritch and Elias. The patients in this study usually showed improvement within several days, resulting in an amelioration of the general condition, no new lesions appearing and resolution of the old lesions. After this stage was reached, a rapid tapering off of corticosteroid dosage was done. Our experience doesn't support the view of Fritch and Elias that it should be done very cautiously.

Snyder and Elias[7] restricted the use of corticosteroid to the first 48-72 hours of the disease. Apparently a significant decrease in both morbidity and mortality were achieved when administered before large, flaccid bullae and large areas of denuded skin are seen. This opinion is confirmed by our experiences. The lost cases were those who came too late for medical aid.

Other authors oppose the administration of corticosteroids. Revus et al. are of the opinion that in some patients necrolysis were completed within 24 hours. Therefore, steroid therapy is illogical in such patients.[1] Garabiol and Touraine in their retrospective study of 27 patients demonstrated an aggravation in the prognosis of patients treated with steroids.[8]

Ruis-Maldorado favoured treating TEN patients without corticosteorids, limiting treatment to administering intravenous fluid and electrolytes, fresh blood and plasma, and handling the patients aseptically. They used antibiotics only in the presence of clinical and laboratory evidence of infection. The mortality rates were 0% of type 1, 37.3 % of type 2, and 60 % of type 3.[4] In our view the case in our series were comparable with type 2 and 3 of the Ruiz-Maldorado series so in conclusion the result I obtained here were somewhat more favourable, the mortality rate being 21.2 %. Revus et al. mentioned a mortality rate ranging from 10,3 % to 70 %.[1] An even lower mortality could be expected in my cases, if aseptic measures were taken in handling the patients.

In spite of views disagreeing to the administration of corticosteroids in the case of TEN, we are still of the opinion that corticosteroid therapy even combined with an antibiotic (the dose of corticosteroids should exceed a 50 mg prednisone equivalent) offers a good prognosis as achieved in this series.

Acknowledgement

The author would like to express his gratitude to Dr. Hendra T Laksman, Jakarta, for his help in editing this paper.

REFERENCES

1. Revus J, Renso D, Roujeau JC et al. Toxic Epidermal Necrolysis. Clinical findings and prognosis factors in 87 patients. Arch Dermat 1987; 123: 1160-5.
2. Golstein SM, Wintroob BW, Illias PM et al. Toxic Epidermal Necrolysis. Arch Dermat 1987; 123: 1153-5.
3. Parsons JM, Virginia R. Management of Toxic Epidermal Necrolysis. Cutis 1985, October : 305-11.
4. Ruiz-Maldorado R. Acute disseminated epidermal necrolysis type 1, 2 and 3. Study of sixty cases. J Am Ac Dermat 1985; 13: 623-35.
5. Heimbach DM, Engav LH, Marvin JA et al. Toxic Epidermal Necrolysis. A step forward in treatment. JAMA Sea 1987; October : 37-42.
6. Kananbroo D, Landgraf WS, Czarnetzki BM. Plasmapheresis in Severe Drug Induced Toxic Epidermal Necrolysis. Arc Dermat 1987; 121: 1548-9.
7. Snyder RA, Elias P. Toxic Epidermal Necrolysis and Staphylococcal Scalded Skin Syndrome. In Jegasothy BV, Lazarus GS. eds. Dermatologic Clinic. Philadelphia : WB Saunders Company 1983; 1/2 : 238-48.
8. Garabiol B, Touraine. Syndrome de Lyell de l'adulte : Elements de pronostic et de'ductions therapeutiques : Etude de 27 cas. Ann Med Interne (Paris) 1976; 127: 670-2. Cited from Snyder.