Tetracycline and Nicotinamide for the Treatment of Bullous Pemphigoid: Our Experience in Singapore

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ABSTRACT

Aim of study: To study the efficacy of tetracycline (or doxycycline) and nicotinamide in the treatment of less extensive bullous pemphigoid.

Methods: An open trial of 11 patients with bullous pemphigoid. Treatment was initiated with tetracycline 1.5-2 g/day and nicotinamide 1.5-2 g/day and gradually tapered down. Doxycycline was substituted for tetracycline in patients who could not tolerate tetracycline due to gastrointestinal side effects or headache.

Results: 6 out of 11 patients achieved complete response (>90% decrease in lesions) while another 2 had partial response (50-90% decrease in lesions).

Conclusion: Tetracycline/doxycycline and nicotinamide is a useful alternative treatment for localized bullous pemphigoid, especially in those whose concurrent medical illnesses preclude the use of systemic corticosteroids.

Keywords: Bullous pemphigoid, tetracycline, nicotinamide

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INTRODUCTION

Bullous pemphigoid is an autoimmune blistering dermatosis affecting mainly the elderly. This relatively benign condition often runs a course of months to years before patients are taken off treatment. The mainstay of treatment is corticosteroids and the use of various immunosuppressive agents for steroid sparing effect. However, these treatments are often associated with morbidity from their side effects. This is particularly prominent among elderly patients who often have other medical conditions and are on polypharmacy.

There have been a handful of case series[1], an open trial[2] and one comparative trial (with prednisolone)[3] reporting the usefulness of nicotinamide and tetracycline in the treatment of bullous pemphigoid. Here, we report on our experience in 11 patients with bullous pemphigoid who were treated with tetracycline/doxycycline and nicotinamide.

METHODS AND PATIENTS

An open trial involving 11 patients was carried out from October 1996 to April 1999. The patients were treated with tetracycline 500 mg tds or qds (1.5-2 g/day) and nicotinamide 500 mg tds or qds (1.5-2 g/day). The lower dosages were given to patients who weighed less than 50 kg. The dosage of tetracycline was maintained until the patient was blister-free for 4 weeks. After that, the dosage of tetracycline was reduced by 500 mg/day per month. Patients who could not tolerate tetracycline were switched to doxycycline, with a starting dose of 100 mg bd, which was then tailed down by 100 mg/day when blister-free for 4 weeks. In a few patients, doxycycline was given in preference to tetracycline for better compliance as they were on multiple drugs for other medical conditions. The initial dosage of nicotinamide was maintained throughout the study period.

When a relapse occurred, the patient was put back on the last effective dosage. When the patient failed to respond to this combination of medication, (failure to respond was defined as development of 5 or more blisters per day), prednisolone was added or substituted. The patients who failed to respond to tetracycline/doxycycline and nicotinamide were also followed up until the 12th week of the trial.

Exclusion criteria were active hepatic, renal and cardiac disease and history of drug allergy to tetracyclines or nicotinamide.

The demographic data, medical history and baseline clinical data were recorded at commencement of the study. Clinical assessment, laboratory investigations and side effects from treatment were obtained at 0, 1, 2, 4, 8 and 12 weeks from the start of the trial. They were then followed up three monthly thereafter.

PROGRESSION OF BULLOUS PEMPHIGOID

The severity of bullous pemphigoid was graded by body surface area involvement. All active lesions, including bullae, urticaria and erosions/crusts were

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included in the assessment. Blister counts, treatment given and all dosage alterations were recorded for each visit.

Complete response (CR) was classified as >90% decrease in lesions, partial response (PR) as 50-90% decrease in lesions, no response (NR) as <50% improvement, and progressive disease (PD) as those who deteriorated on treatment.

MONITORING

The blood pressure and laboratory investigations were monitored throughout the study. Patients were also monitored for other adverse effects arising from therapy.

RESULTS

Of 11 patients who were enrolled into the study, 6 were male and 5 female. The average age of the patients was 70.0 years (men 71.5 years, women 68.2 years). The race distribution was: 7 Chinese, 1 Eurasian and 3 Indians. The average duration of disease before treatment was 5.3 months (Range 0-36 months). None of the patients had received any systemic therapy before the study. 9 out of 11 patients were also on mid-potency topical steroid therapy, i.e. betamethasone valerate 0.05%-0.1% cream, during the study period.

The diagnosis of bullous pemphigoid was based on a combination of clinical, histological and immunopathological features. All the cases showed subepidermal blistering with intact epidermis forming the roof, eosinophil-rich inflammatory infiltrate in the dermis, and linear deposits of C3 and IgG on direct immunofluorescence studies. The indirect immunofluorescence was done in 9 patients, 6 had positive roof pattern, 1 showed positive floor pattern and 2 were negative although they had not received any prior therapy.

7 out of the 11 patients completed the treatment and follow-up (Table I). One of the patients who did not complete the follow up defaulted after week 8, when he achieved clearance of his skin lesions. This patient subsequently suffered a relapse four months after stopping therapy. He has since passed away from pneumonia one month after the onset of relapse of disease. Three more patients had to stop treatment, two due to progression of disease and the other one due to the vomiting and diarrhoea from tetracycline.

Of the patients who improved on tetracycline/ doxycycline and nicotinamide therapy, six had near complete clearance of their skin lesions, while two had partial clearance. The mean duration of clearance for complete responders was 6.0 weeks, while those who were partial responders had maximal clearance by 12 weeks. There was one patient who experienced neither improvement nor deterioration during the treatment period – prednisolone 30 mg/day was added at week 10 of the study.

The extent of disease ranged from 1% to 40% of body surface area involvement. 8 out of 11 patients had less than 15% involvement of body surface area. Of the three patients with more extensive involvement, i.e. >15% of BSA, one had responded completely with doxycycline/ nicotinamide therapy, another had partial response to tetracycline/ nicotinamide and a third patient had failed doxycycline/nicotinamide, requiring prednisolone and dapsone to control his disease. Of the six patients who had achieved a complete response,

Table I. Summary of treatment responses and adverse effects.

No. of patients	Treatment	Response	Side effects	Outcome
5	Tetracycline/ nicotinamide	CR - 4	GIT - 2 Headache - 1	1 switched to doxycycline at week 12 but relapsed at week 14, 1 who had cleared at week 2 was switched to prednisolone 30mg at week 4 due to vomiting from tetracycline, with no subsequent relapse.
		PR - 1	GIT - 1	Switched to doxycycline at week 6 with no relapse.
6	Doxycycline/ nicotinamide	CR - 2	0	No relapse.
		PR- 1	0	Continued treatment till defaulted after 6 months of therapy but had stopped having blisters.
		NR - 1	0	Prednisolone 30mg/day added at week 10 and doxycycline/nicotinamide taken off after 6 months.
		PD - 2	0	1 controlled with prednisolone 45mg/day, another controlled with prednisolone 60mg/day + dapsone 100mg.

Complete response (CR) – >90% decrease in lesions
Partial response (PR) – 50-90% decrease in lesions
No response (NR) – <50% improvement
Progressive disease (PD) – those who deteriorated on treatment

the mean initial area of involvement was 4% of the total body surface area, while that of the five patients with partial response or worse was 8%. This was not statistically significant.

Out of 6 patients who were complete responders, 4 received treatment with tetracycline and two had doxycycline. Of the 2 partial responders, one was treated with tetracycline and the other was on doxycycline. Of the 3 remaining patients who had no improvement or progression of disease, all were treated with doxycycline.

There was a significant rate of side effects observed, particularly to tetracycline, with 3 patients developing vomiting or retching, one of these patients had diarrhoea as well, and a fourth patient developed headache. There were no complaints of flushing due to nicotinamide among the patients in this study. None of the patients on doxycycline reported adverse effects.

Of the 6 patients with complete response to tetracycline/doxycycline and nicotinamide, 2 relapsed after completion of the study. Both had achieved complete response. One relapsed at 14 weeks while still on doxycycline and nicotinamide. The other relapsed six months after stopping doxycycline and nicotinamide therapy.

DISCUSSION

The mainstay of therapy for bullous pemphigoid has been systemic corticosteroids. However, most patients are elderly, and have concurrent medical problems such as diabetes mellitus, hypertension, congestive cardiac failure and osteoporosis, which may be aggravated by corticosteroid therapy. The use of immunosuppressive drugs as steroid sparing agents is also associated with serious side-effects which are poorly tolerated by the elderly.

Berk and Lorincz[1] first reported success in the treatment of bullous pemphigoid with a combination of tetracycline (up to 2 g/day) and nicotinamide (up to 2.5 g/day) in 1986. Such high doses may have significant side effects in the elderly population, especially for the smaller Asian build. We have therefore initiated lower dosages for those weighing less than 50 kg in this study. Since then, there have been a few more studies which have demonstrated the effectiveness of this treatment in this disease.

Fivenson et al[3] published the results of a randomized controlled study which compared this combination treatment with prednisone. Of 12 patients on tetracycline and nicotinamide, there were five complete responders, five partial responders, one non-responder and one who had disease progression. Of the 6 patients on prednisone, there was one complete responder and five partial responders. In their study, they also noted that the efficacy of tetracycline and nicotinamide was independent of the extent of disease.

Kolbach et al[2] reported reduction of blister formation within 1-2 weeks and cessation of bulla formation within 6-8 weeks in 7 patients treated with tetracycline and nicotinamide. In our study, clearance was seen within 6 weeks for complete responders.

In a brief communication, Hornschuh et al[4] treated 16 patients with oral tetracycline and nicotinamide combined with the initial application of 0.5% clobetasol propionate cream, which was added on for more rapid effect. Complete clearance of skin lesions was seen in 13 patients within 4 weeks of treatment. One patient responded completely only after 5 months and there were 2 non-responders.

The mechanisms of effect for these two drugs are not known yet. However, there are a variety of proposed mechanisms. Nicotinamide may act as an electron scavenger[5], phosphodiesterase inhibitor[6] or stimulator of tryptophan conversion to serotonin[7,8]. It also acts as a histamine receptor antagonist as well as an inhibitor of histamine release[9-13]. Tetracycline has been reported to increase cohesion of the epidermal basement membrane zone[14]. Both drugs have also been shown to inhibit neutrophil and eosinophil chemotaxis and secretion[1,13,15-18].

There have been a few reports of successful treatment of bullous pemphigoid with tetracycline alone[19-21]. Thomas et al[20] reported a small series of five patients in whom blister formation was stopped and reepithelialization completed within two months on oral tetracycline and a midpotency topical steroid. They concluded that tetracycline was rapidly effective and devoid of toxicity in bullous pemphigoid.

There have been no studies of treatment of bullous pemphigoid with nicotinamide alone. Neither has there been a study comparing tetracycline alone against the combination therapy of tetracycline and nicotinamide.

There has been one report in which no response was seen in two patients with bullous pemphigoid who were treated with doxycycline alone[22]. No studies have been done so far to assess the efficacy of combination therapy with doxycycline and nicotinamide.

CONCLUSION

Treatment with tetracycline and nicotinamide for bullous pemphigoid is effective in 6 out of 11 patients treated in this study. This is a useful alternative treatment especially in the elderly whose medical conditions preclude the use of corticosteroids. Our observation is that patients with more localized disease respond better than those with widespread disease. Doxycycline is preferred to tetracycline by patients as it has fewer gastrointestinal side effects and a more convenient dosing.

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