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Combination therapy with nicotinamide and tetracyclines for cicatricial pemphigoid: further support for its efficacy

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Summary

We have previously reported the reduction of cicatricial pemphigoid orodynia with minocycline. Tetracycline combined with high dose nicotinamide has also been beneficial in a number of cutaneous immunological disorders. We now report a series of eight cases in whom further subjective or clinical improvement accrued in five, after the addition of high dose (2·5 or 3 g) nicotinamide to minocycline; however, one of these then discontinued the nicotinamide because of headache and nausea, another was withdrawn from the study because of progressive upper respiratory tract mucosal involvement, and two were changed from minocycline to tetracycline because they developed minocycline-induced hyperpigmentation.

Cicatricial pemphigoid is an autoimmune blistering disease[1] predominantly affecting the mucosae of elderly people. The oral, ocular or genital mucous membranes, and also the skin, are frequently involved. The condition may cause marked discomfort and can result in scarring and disabling stricture formation. Many patients have disease that is difficult to treat or have associated side-effects from drugs; conventional treatment involves steroids, immunosuppressive therapy and dapsone, each of which requires close monitoring.[2–5] We have also previously reported a therapeutic benefit in cicatricial pemphigoid from minocycline therapy alone,[6] whereas Berk and Lorinez reported success from combined tetracycline and niacinamide in bullous pemphigoid,[7] and further studies have supported this.[8,9] Furthermore, Chaffins *et al.* reported success with nicotinamide and tetracycline together in 13 cases of pemphigus and linear IgA disease.[10] We now report our findings with the addition of nicotinamide to minocycline or tetracycline in eight patients with cicatricial pemphigoid in an open nonplacebo controlled study.

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Methods

Cicatricial pemphigoid (CP) patients attending the outpatients departments of dermatology at Amersham General Hospital, Buckinghamshire and the Oxford Radcliffe Hospital, Oxford, and who had been taking tetracycline for a period of at least 12 weeks without adequate symptomatic control, were invited to participate. One patient (Case 7) had been changed from minocycline to oxytetracycline several months prior to entry into the study because of minocycline-induced pigmentation of the lower legs, while the remainder (of whom Cases 5 and 6 have been discussed previously in case reports[11,12]) had been on minocycline 100 mg daily. Patients with significant liver function test abnormalities on preliminary testing were excluded and liver function tests were performed every 3 months. The study was approved by the research ethics committee in each hospital.

Patients were commenced on 500 mg of nicotinamide daily, the dose then being increased by 500 mg increments at 2-week intervals until symptomatic control was achieved or a maximum of 3 g daily had been reached, usually by 10–12 weeks. Each patient was reviewed at 4–6 week intervals. Two visual analogue scales of 0–9 were recorded at each visit to evaluate symptoms (where 0 represented no symptoms and 9 the worst symptoms they had ever experienced), firstly at the time of the visit and secondly as an average over the preceding month; the average was then calculated from these two scores. The number and size of the lesions was also recorded as small (<0·5 cm), medium (0·5–2·0 cm) or large (>2·0 cm), and a photographic record kept of each visible lesion. Once symptomatic control, or the maximum dose of 3 g, was reached the patient was maintained on nicotinamide for 6 months before the dose was weaned off. Scores prior to treatment, after the maximum dose of nicotinamide had been taken for 6 months, and 4 months after discontinuation of the nicotinamide were then compared.

Results

Eight patients were entered into the trial, seven of whom

Table 1. Response of CP patients response to 6 months of nicotinamide (2.5–3 g) added to minocycline 100 mg or tetracycline 1 g

Case	Age (years)	Sex	Visual analogue score			Lesions pre-nicotinamide			Clinical progress
			Before*	During†	After‡	Site	Size	Number	
1	68	M	6	6	5	Gingiva	Small	10	Improved
2§	62	F	7	5	5	Palate	Small	3	Improved
						Gingiva	Small	3	Improved
						Conjunctiva	Small	3 Blisters	Nil
3	73	M	5	4	4	Palate	Medium	2	Stopped
						Forehead	Small	1	Nausea
						Chin	Small	1	
4	68	M	4	4	4	Buccal mucosa	Small	4	Varied
						Gingiva	Small	2	Improved
						Groin	Medium	1	Resolved
5§	71	F	6	4	4	Buccal mucosa	Small	2	Resolved
						Palate	Small	2	Improved
						Vulva	Large	1	Unchanged
						Leg	Small	1	Evolved
6	72	F	6	4	4	Buccal mucosa	Small	2	Resolved
						Vulva	Medium	7	Improved
						Perianal	Medium	3	Improved
						Cutaneous	Medium	Extensive cutaneous disease	Improved
7	71	F	5	4	4	Conjunctiva	Small	1	Improved
						Buccal mucosa	Small	3	Improved
						Vulva	Small	2	Improved
						Perianal	Small	4	Unchanged
8	62	F	6	7	6	Buccal mucosa/ pharynx	Small	1 Discomfort	Improved epiglottic ulcers/stridor

*Pre-nicotinamide.
†After 6 months' nicotinamide treatment.
‡Four months after stopping nicotinamide.
§Changed from minocycline 100 mg to tetracycline 500 mg twice daily, mid-treatment, because of minocycline pigmentation.

tolerated nicotinamide well; however, Case 3 discontinued the drug after 2 weeks of 1 g per day because of dizziness and nausea; these symptoms then improved within 5 days. Symptoms related to his CP did not change during the medication period.

Cases 1 and 5 increased their doses of nicotinamide up to 3 g, whereas the remainder reached a maximum dose of 2·5 g. None of these patients experienced any adverse effects and there were no liver function abnormalities detected in any patient during the study.

All patients (except Cases 3 and 8) derived marked clinical improvement during and for 4 months after the course of nicotinamide (Table 1); of these, subjective (visual analogue score) improvement was noted in five patients (cases 1, 2, 5, 6, 7). Case 4 remained unchanged, Case 5 was the only patient to develop a new lesion (small leg erosion) during the study period and Case 6 had extensive cutaneous disease, including bilateral palmar involvement, and this, together with oral and genital ulceration, was improved by nicotinamide and minocycline combination therapy after 2 months. Case 7 had perianal ulceration that was resistant to therapy, while the oral and conjunctival disease responded to combination therapy. The perianal disease was however complicated by haemorrhoids which required surgical excision during the study period. Nicotinamide was discontinued in Case 8 after 12 weeks because of the development of progressive upper respiratory tract mucosal involvement causing stridor: ulceration of the epiglottis was visible at bronchoscopy and high dose oral steroid therapy and tracheostomy was required to control the symptoms.

Two of the patients (Cases 2 and 5) also developed unacceptable minocycline-induced hyperpigmentation during the study and were therefore changed to tetracycline 1 g daily instead.

Discussion

Nicotinic acid is a vitamin (B_3); it is converted to nicotinamide in the body and then functions as an essential coenzyme, accepting hydrogen ions in tissue respiration oxidation–reduction reactions.[13] Nicotinamide also inhibits

serum phosphodiesterase, resulting in increased cyclic adenosine monophosphate (cAMP) concentrations and, in turn, reduced protease release from leucocytes.[13] In addition, it inhibits antigen-induced lymphocyte proliferation and transformation,[14] neutrophil and eosinophil chemotaxis and secretion,[10] mast cell histamine release and is a free radical scavenger. Such properties may account for its apparent beneficial effects in a wide variety of immunological and inflammatory skin diseases; thus a number of these have benefited from high dose (300–2500 mg/day) therapy, particularly dermatitis herpetiformis,[15] erythema elevatum diutinum,[16] generalized granuloma annulare,[17] various immunobullous diseases,[6–12] polymorphic light eruption,[18] and necrobiosis lipoidica.[19] Cicatricial pemphigoid is also an immunological mucosal and cutaneous disorder, the *in vivo* deposition of immunoglobulins and complement at the basement membrane zone with the presence of circulating basement membrane zone antibodies providing the evidence for an autoimmune aetiology.

Nicotinic acid, the precursor of nicotinamide, however, has been associated with liver function abnormalities when used in large doses (3–10 g/day) in the treatment of hypercholesterolaemia.[20–25] Reversible hepatic toxicity has been reported once, following the use of 9 g/day of nicotinamide. Nevertheless we detected no liver function abnormalities in our eight cases. Furthermore, unlike nicotinic acid, nicotinamide is not a potent vasodilator and does not cause flushing[14] or impair glucose tolerance. It is possible that higher doses of the drug could produce further clinical improvement than we have reported in our cases, but a closer monitoring of liver function tests would then be advised. It would also seem prudent to monitor the liver in all patients receiving long-term, high dosage therapy. We have also previously reported a high prevalence of minocycline-induced hyperpigmentation in CP patients, who are also often elderly,[6] and a further two cases (2 and 5) developed this problem during this study.

Tetracyclines suppress leucocyte chemotaxis *in vitro* and *in vivo* at therapeutic concentrations and this is their proposed mechanism of action in inflammatory skin disease.[7] We have also previously discussed the immunological effects of this drug[3] and postulated that the combined effect of both minocycline and nicotinamide in blast transformation inhibition and the inhibition of neutrophil and eosinophil chemotaxis could serve to downgrade both the afferent and efferent limbs of humoral immune responses.[11] Such mechanisms could therefore explain the clear additional benefit that we have shown by the addition of high dose nicotinamide to minocycline (or tetracycline) in CP.

CP is a rare disease which runs a variable course and the acute features of discomfort and ulceration are prone to spontaneous relapses and remissions. Objective clinical assessment is thus very difficult. For these reasons we measured the clinical response subjectively with visual analogue scales, and clinically by recording the number of lesions, measuring their size and keeping photographic records. We further chose a 6-month period of assessment as a reasonable time frame to incorporate the effects of such a fluctuating disease. However, this was a pilot, nonplacebo controlled study, and should now be followed by a double blind cross-over investigation. The striking advantage that nicotinamide and tetracycline combination therapy has over treatment with corticosteroids and other immunosuppressive agents is their better side-effect profile in a disease which frequently requires prolonged therapy over many years. In the light of the dramatic clinical benefits shown in this study, therefore we felt these preliminary results should be reported.

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