ANTIBIOTICS USED AS ANTI-INFLAMMATORY AND IMMUNOMODULATORY AGENTS IN DERMATOLOGICAL DISORDERS

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ABSTRACT

BACKGROUND

Antibiotics are the drugs used for killing or inhibiting growth and multiplication of infectious organisms. Antibiotics are commonly prescribed for treatment of infections. However, antibiotics have immunomodulatory and anti-inflammatory properties and can be used for various non-infectious dermatoses. Dermatologists routinely prescribe antibiotics in treatment of various non-infectious disorders. Tetracyclines can be used in Bullous pemphigoid, Acne vulgaris, Rosacea, Hidradenitis suppurativa, Pyoderma gangrenosum, Linear IgA disease and Dermatitis herpetiformis.[1]

This clinical study will review anti-inflammatory and immunomodulatory effects of Tetracyclines used in 15 patients of bullous pemphigoid (04), acne vulgaris (06), pyoderma gangrenosum (03) and rosacea (02) along with vitamin B3 (niacinamide). These drugs can be used as steroid sparing agents when other comorbidities are present in elderly patients.

KEY WORDS

Antibiotics, Anti-Inflammatory, Immunomodulatory, Dermatological Disorders.

HOW TO CITE THIS ARTICLE: Ali SS, Praveena T, Lata MM, et al. Antibiotics used as anti-inflammatory and immunomodulatory agents in dermatological disorders. J. Evolution Med. Dent. Sci. 2018;7(34):3804-3807, DOI: 10.14260/jemds/2018/853

BACKGROUND

Antibiotics are chemicals derived from microorganisms that have the capacity to kill other microorganisms (Bacteria, virus, fungi and parasite) or inhibit their growth. In routine clinical practise, antibiotics are chiefly used to eliminate various microorganisms (Bacteria, viruses and parasites). Many antibiotics were found to have anti-inflammatory properties.[2-5]

Tetracyclines

The tetracyclines are broad-spectrum antibiotics and comprises of four main drugs Tetracycline [T], doxycycline [D], minocycline [M] and lymecycline [L]). These antibacterial agents are indicated in a wide range of infections including Treponema pallidum (Syphilis), Borrelia burgdorferi, Borrelia garinii (Lyme disease), Coxiella burnetii (Q fever), Rickettsia rickettsii (Rocky Mountain spotted fever) and Yersinia pestis (Plague). Their antibiotic effect is by binding to the 30S subunit of bacterial ribosomes and halting protein synthesis. However, many tetracyclines have anti−inflammatory properties.[6-7] Alteration of Tetracycline structure may alter phototoxic potential, which is dose related phenomenon, more common with Doxycycline >Tetracycline > Minocycline.

In dermatology, Tetracyclines are commonly used in Acne vulgaris. More recently, biologic actions affecting inflammation, proteolysis, angiogenesis, apoptosis, metal chelation, ionophoresis and bone metabolism have been researched. The therapeutic effects of tetracycline include rosacea, bullous dermatoses, neutrophilic dermatoses, pyoderma gangrenosum, sarcoidosis, aortic aneurysms, cancer metastasis, periodontitis and autoimmune disorders such as rheumatoid arthritis and scleroderma.

Anti-inflammatory properties include: 1. Inhibition of the production of neutrophil chemoattractants by P. acnes; 2. Inhibition of neutrophil migration; 3. Inhibitory activity against granuloma formation in vitro, due to protein kinase C inhibition; 4. Inhibition of multiple matrix metalloproteinases (MMP); 5. Down regulation of cytokines of innate immune response; and 6. A possible scavenger effect against reactive oxygen species (ROS).[6-7]

Disease/ Condition	Agent	Mechanism of Action for Anti-inflammatory Property	Dose
Acne vulgaris	D, M	Inhibits IL-8[8] Inhibits MMP-1[9] ROS scavenging[10-11] Inhibiting bacterial products that stimulate inflammation[12-13]	
Confluent and reticulated papillomatosis[14] Granulomatous diseases[15]	M D, M	Inhibit T-cell proliferation and granuloma formation[16]	D-200 mg/day M-200 mg/day
Immunobullous diseases[17-19]	T, M D	Inhibit MMP and mast cell activation[20]	T-1500 mg/day M-100 mg/day D-100 mg/day
Neutrophil disorders [21,22]	D, M	Inhibit IL-8 and neutrophil activation[23]	D-200 mg daily M-200–300 mg/day
Rosacea[24]	D, M	Decreases ROS damage[23] Act on VEGF, iNOS and NO and preventing excessive vascular dilatation and angiogenesis in rosacea[25]	D-100 mg/day M-100 mg/day

'Financial or Other Competing Interest': None.
Submission 16-05-2018, Peer Review 01-08-2018,
Acceptance 09-08-2018, Published 20-08-2018.
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DOI: 10.14260/jemds/2018/853

		Inhibit granuloma formation in vitro[11]	
Lichen planus[26]	T, D	Inhibition of the T-lymphocyte response(27)	T-500 mg BD, D-100 mg BD.
Pityriasis lichenoides[28]	T	Inhibition of the T-lymphocyte response[18]	500 mg BD
Prurigo pigmentosa[29,30]	D, M	Inhibits the migration and/or function of neutrophils[23]	D-200 mg/day M-200 mg/day

Table 1. Indications of Tetracyclines in Dermatology as Anti-Inflammatory Drugs

BD: Twice a day, OD: Once a day, D: Doxycycline, M: Minocycline, ROS: Reactive oxygen species, NO: Nitric oxide, iNOS: Inducible Nitric Oxide Synthase, VEGF: Vascular Endothelial Growth Factor, IL: Interleukin, MMP: Matrix Metalloproteinase, T: Tetracycline, L: Lymecycline

Niacin (Vit B_3)

Niacin is an essential dietary constituent, the deficiency of which leads to pellagra. In the body nicotinic acid is converted to niacinamide, which functions as a coenzyme that accepts hydrogen ions in oxidation-reduction reactions essential for tissue respiration.

Anti-inflammatory effect of niacinamide, it inhibits poly-(ADP-ribose) polymerase-1 (PARP-1), a nuclear enzyme that enhances nuclear factor-κB transcription. Inhibition of this pathway alters leukocyte chemotaxis by dysregulation of adhesion factors necessary for migration.[31] Niacinamide reduces lysosomal enzyme release and stabilises leukocytes by inhibiting cAMP PDE, and also inhibits lymphocytic transformation and the production of antibodies. This latter mechanism makes the drug particularly useful for the treatment of antibody-mediated diseases (e.g. bullous pemphigoid).

In immunobullous disorders, one randomised, open-label trial suggested comparable efficacy and fewer adverse effects using the combination of nicotinamide (niacinamide) and tetracycline compared with prednisone as first-line therapy for bullous pemphigoid.[32] Another small review suggested that the combination of nicotinamide and tetracycline may be an effective alternative to corticosteroids in pemphigus foliaceus and pemphigus erythematosus and as a 'steroid-sparing' adjuvant rather than corticosteroid alternative in pemphigus vulgaris.[32] Assessment of clinical response to niacinamide alone in treating autoimmune blistering disorders and erythema elevatum diutinum has clearly been complicated by concomitant tetracycline or erythromycin use in these studies. It has been proposed that the anti-inflammatory properties of these antibacterial agents may function synergistically with nicotinamide in the treatment of diseases with excessive PMN chemotaxis.[33] Because tetracycline alone has been reported to clear bullous pemphigoid, it is difficult to assess nicotinamide's exact contribution in treatment of bullous diseases.[34] However, one case of localised bullous pemphigoid responding to niacinamide alone has been reported.[35]

Aim

Treatment of bullous pemphigoid, pyoderma gangrenosum, acne vulgaris and rosacea with doxycycline and niacinamide.

MATERIALS AND METHODS

An open trial on 15 patients treated with Doxycycline and niacinamide. Doxycycline, with a starting dose of 100 mg bd, which was then reduced by 100 mg/day. The initial dosage 500 mg bd of niacinamide was maintained throughout the study period, from February 2017 to November 2017. When a relapse occurred, the patients were treated again with the last effective dosage. When the patient did not respond to medication (failure to respond with development of 5 or more lesions per day), prednisolone was added in bullous pemphigoid and pyoderma gangrenosum patients, whereas in acne vulgaris and Rosacea patients, retinoids were added.

Exclusion criteria was patients with hepatic disease, kidney diseases, cardiac disease, pregnant women, nursing mothers and patients allergic to Doxycycline and niacinamide. Detail history of the patients with vitals was recorded at time of initial treatment. Clinical examination, blood investigations and adverse events from treatment were recorded at 0, 4, 8 and 12 weeks. Then patients were followed every three months once. The severity of disease was based on body surface involvement and active lesions like blisters, wheals, papules, pustules, nodules, ulcer, erosion and crusts. Complete improvement (CR) was recorded as > 90% improvement in lesions, partial improvement (PR) as 50-90% improvement in lesions, no response (NR) as < 50% improvement and progressive disease (PD) as those who did not respond to treatment.

Monitoring

Blood investigations and vital parameters were recorded throughout the study. Child bearing female age group were strictly monitored for pregnancy test. Patients were monitored for any adverse reactions with medications.

RESULTS

15 patients were treated in the clinical study, 8 were males and 7 were females. The mean disease duration prior to onset of treatment was 5.3 months (Range 0 - 36 months). Clinically, bullous pemphigoid was diagnosed and confirmed with skin biopsy and histopathology report. Four patients of bullous pemphigoid were treated with Doxycycline and niacinamide along with topical treatment. Three patients had good improvement and one patient did not come for follow-up defaulted.

Three patients with pyoderma gangrenosum diagnosed based on clinical, histological features and treated with DOX + NIA along with topical treatment, one had complete clearance of lesions, one patient had partial clearance and treatment continued for six months. One patient with no improvement with medication prednisolone 30 mg/day was added after study period.

Six patients with acne vulgaris with grade II and III were treated with DOX + NIA along with topical medication, five patients had complete clearance, whereas one patient with grade III acne vulgaris improved partially and subsequently oral isotretinoin 10 mg/day was started. Two patients with papulopustular rosacea was treated with partial clearance and subsequently started with oral retinoids.

The average duration of complete improvement was 8.0 weeks, while those with partial improvement had complete improvement at 12 weeks. Severity of disease was ranged from 10% to 40% of BSA. 10 patients of study had less than

15% involvement of BSA. Five patients with severe disease involvement, i.e. > 15% of BSA. No adverse drug reactions were observed with doxycycline and niacinamide in all 15 patients.

No. of Patients	Disorder	Treatment	Response	Side Effects	Out come
4	Bullous pemphigoid	Doxycycline + Niacinamide	CR-3	No	No relapse
			CR-1	No	After 2 months patient default
3	Pyoderma gangrenosum	Doxycycline + Niacinamide	CR-1	No	No relapse
			PR-1	No	Treatment continued till 6 months
			NR-1	No	Prednisolone 30 mg/day started at 8th week
6	Acne vulgaris	Doxycycline + Niacinamide	CR-5	No	No relapse
			PR-1	No	Subsequently oral isotretinoin 10 mg/day at 10th week
2	Rosacea	Doxycycline + Niacinamide	PR-2	No	Subsequently oral isotretinoin 10 mg/day started at 10th week

Table. 2 Treatment responses and adverse reactions in the Study

Complete improvement (CR) – > 90% decrease in lesions; Partial improvement (PR) – 50 - 90% decrease in lesions. No improvement (NR) – < 50% improvement

DISCUSSION

The mainstay of treatment for bullous pemphigoid and pyoderma gangrenosum is systemic corticosteroids. However, some patients are elderly and have concurrent diabetes mellitus, hypertension, congestive cardiac failure and osteoporosis, which maybe 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[36] first reported success in the treatment of bullous pemphigoid with a combination of tetracycline (upto 2 g/day) and nicotinamide (upto 2.5 g/day) in 1986. Fivenson et al[32] published the results of randomised controlled study, which compared this combination treatment with prednisone. Of 12 patients on tetracycline and nicotinamide, there were five complete responders, five partial responders and one non-responder.

Kolbach et al[37] reported improvement with decrease of blister formation within 6 - 8 weeks in 7 patients treated with tetracycline and nicotinamide. In our study, improvement was observed within 8 weeks. Hornschuh et al[4] treated 16 patients with oral tetracycline and nicotinamide combined with the initial application of 0.5% clobetasol propionate cream. Complete improvement of skin lesions was seen in 13 patients within 4 weeks of treatment. In our study 4 patients with bullous pemphigoid was treated with Doxycycline 100 mg BD and Niacinamide 500 mg BD, three patients had complete improvement after 12 weeks treatment, one patient had complete improvement after 8 weeks, but lost for follow-up by default.

The successful use of minocycline in pyoderma gangrenosum A report of seven cases and review of the literature by Berth-Jones J[22]. Successful treatment of Sweet's syndrome with doxycycline by Joshi RK[21], In our study 3 patients with Pyoderma gangrenosum treated with DOX + NIA, of which 1 had complete clearance of lesions, 1 patient had partial clearance at the end of 12 weeks so treatment continued with DOX + NIA for three months and one patient had poor response so oral prednisolone 30 mg/day was started at 8 week.

Six patients with acne vulgaris were treated, of which 5 patients had complete clearance of lesions and one patient had partial response subsequently oral retinoids started with 10 mg/day at 12 weeks.

Sneddon performed a double-blind, placebo-controlled trial of tetracycline for rosacea in 1966 to evaluate its effects on the "erythematous and papular type" and the "pustular form" of rosacea.[38] The second-generation tetracyclines are similarly effective for rosacea, In our study, two patients with papulopustular rosacea was treated with partial clearance of lesions at 12 weeks, subsequently systemic retinoids started.

CONCLUSION

Treatment with Doxycycline and niacinamide as anti-inflammatory and immunomodulatory agents for dermatological disorders is effective in 10 out of 15 patients treated. This is an effective steroid sparing treatment regimen in the elderly patients with other comorbidities. Doxycycline with Niacinamide can be used in some immune disorders of dermatological conditions. In our study, patients with more localised disease respond better than those with widespread disease. Doxycycline and Niacinamide have lesser gastrointestinal side effects and a more convenient dosing with more compliance of patients.

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