Sulphapyridine—a new agent for the treatment of ocular cicatricial pemphigoid

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Abstract

Aims—Ocular cicatricial pemphigoid (OCP) is a severe, potentially sight threatening systemic disease that sometimes requires systemic immunosuppression. This study assessed the clinical outcome of patients with OCP treated with sulphapyridine, a sulphonamide with an anti-inflammatory and immunosuppressive action but few side effects.

Methods—A prospective, single armed, unmasked clinical trial was undertaken at Moorfields Eye Hospital. Twenty consecutive patients with moderate or marked conjunctival inflammation due to OCP were treated with oral sulphapyridine 500 mg twice daily. The degree of ocular inflammation was assessed as nil, mild, moderate, marked, or severe. Success was defined as resolution to mild or less. Ocular limbitis, systemic features of the disease, and side effects of the drug were also monitored.

Results—Follow up was a mean of 12.3 (SD 4.0) months and ranged from 7 to 17 months. A successful reduction in inflammation was recorded in 22/39 eyes (56%) and 10/20 patients (50%). This improvement occurred within 1 month in 64% and in all by 2 months. Three patients developed allergy. Other side effects included nausea (n=3), headache (n=1), urinary hesitancy (n=1), and mild lymphocytopenia (n=1). These were dose dependent. Progression of cicatrization was observed in 1/22 eyes. Success was less likely if there were systemic features of OCP or ocular limbitis.

Conclusions—Sulphapyridine was clinically effective in 50% of patients with moderate marked inflammation and had few side effects. It is a good alternative to dapsone.

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Ocular cicatricial pemphigoid (OCP) is a severe, bilateral sight threatening systemic disease characterised by recurrent conjunctivitis and blistering of the skin and mucous membranes. Typically one third of patients become legally blind.¹ The majority of patients have ocular involvement and approximately 50% develop systemic manifestations.^{2,3} Therefore, the disease has features of both the cicatrizing conjunctivitis and of the bullous skin diseases.

The key ocular features of OCP are conjunctival inflammation and subconjunctival fibrosis. The majority of cases have progressive fibrosis which can result in cicatricial entropion and trichiasis, corneal epithelial dysfunction, keratoconjunctivitis sicca, and corneal opacification. Most cicatrization occurs during active inflammation.^{2,4,5}

The objectives of management are short and long term. In the short term, patients require amelioration of their symptoms and ocular surface disease signs. In the long term, the objective is to prevent progression of the cicatrization to minimise ocular morbidity and maximise visual function. These objectives may sometimes be met with topical ocular treatment. However, systemic disease or severe ocular disease requires systemic treatment. Effective agents include dapsone, high dose steroids, azathioprine, and cyclophosphamide. Unfortunately, treatment may be needed for several years and the majority of patients are elderly. These factors contribute to reduced tolerance.

This prospective study aimed to assess the role of oral sulphapyridine in OCP. Sulphapyridine has not previously been used for OCP, but it has been successful in other inflammatory dermatoses^{6,7} and in rheumatoid arthritis.⁸⁻¹¹ It has also been used for inflammatory bowel disease when combined with 5-aminosalicylic acid (5-ASA).¹²⁻¹⁵ Sulphapyridine was chosen for the study because it is an effective anti-inflammatory and immunosuppressive agent for similar diseases and has fewer side effects than the existing agents.

Materials and methods

Patients were selected for the study from the corneal and external disease clinics at Moorfields Eye Hospital over the 18 month period from September 1992. All patients with OCP were categorised from 0 to 4+ by the amount of conjunctival inflammation. These were defined as mild (+), conjunctival hyperaemia only; moderate (++) , hyperaemia with conjunctival oedema; marked (+++) , significant conjunctival stromal and epithelial oedema; severe (++++), very oedematous conjunctival stroma and epithelium in four quadrants.^{2,16} The inclusion criteria were all patients with OCP who had 'moderate' to 'marked' ocular inflammation that had either failed to respond to topical treatment (n=17) or dapsone (n=3). All patients were consecutive and there were no exclusions. All patients had bilateral inflammation of a moderate degree or worse, except

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for one. Other causes of conjunctival inflammation such as lid margin disease and trichiasis were managed until resolved before entry into the study. Conjunctival biopsy was performed on all but two patients and was defined as positive if there was immunofluorescent basement membrane deposition of IgG, IgA, or complement. Appropriate positive and negative controls were used. Patients who were biopsy negative had characteristic subepithelial fibrosis and progressive conjunctival cicatrization. A proforma was used to record the data prospectively using the same observers.

The presenting ocular signs were staged according to the two systems of Mondino and Foster.^{5 16-18} Foster's stages are based on specific clinical signs: stage 2, fornix shortening; stage 3, symblepharon; stage 4, ankyloblepharon. Mondino's stages are based on the lower fornix depth—for example, stage 3 is a loss of depth of 50–75%. This depth was measured optically with a normal depth being defined as 11 mm.¹⁹ The eyes were Foster's stages II–IV in 4/40, 36/40, and 0/40 eyes and Mondino's stages II–IV in 8/40, 17/40, and 15/40 eyes, respectively. Limbitis was defined as a raised, inflamed region involving the limbal tissues extending for one quadrant or more.

All patients were treated with oral sulphapyridine 500 mg twice daily as the sole systemic agent (May & Baker, Rhone-Poulenc Rorer Ltd, Dagenham). No other systemic or topical treatment was altered when the sulphapyridine was started except for the three patients who had their dapsone stopped. No patient was known to be allergic to sulpha drugs. Success was defined as an objective improvement in the inflammation to just detectable (+) or less. Patients were assessed at monthly intervals for 3 months and 2 monthly thereafter. Full blood counts were obtained at each visit. A significant haematological change was defined as greater than 10% from the baseline. A proforma was used to record the data prospectively with the same observer (MJE) for all patients over the 18 months. Statistical analysis used χ^2 with Yates's correction.

Results

Twenty consecutive patients with ocular inflammation of ++ or +++ were enrolled. This involved 39 eyes. The mean age was 74.5 (SD 8.6) years and ranged from 53 to 86 years. Twelve patients were men, 14 patients had a positive biopsy. No patient was on oral anti-inflammatory agents or oral steroids. Topical medication, excluding lubricants, included steroids (n=6 patients), acetylcysteine (n=1), and retinoic acid (n=1). Ocular and systemic features of the successful and unsuccessful groups, at the time of initiating the sulphapyridine, are detailed in Tables 1 and 2. These groups exclude three cases of allergy because the treatment duration was too short to assess its effect. The one eye that initially had only mild (+) inflammation had total resolution of the inflammation. Only Mondino's staging was useful at discriminating between the two groups because of the predominance of

Table 1 Initial ocular status and response to sulphapyridine (per eye)

	Overall (n=40)	Successful (n=22)	Unsuccessful (n=11)
Mondino's stages			
II	8/40	1/22	1/11
III	17/40	12/22	6/11
IV	15/40	9/22	4/11
Inflammation			
+	1/40		
++	17/40	8/22	5/11
+++	23/40	14/22	6/11
Limbitis	6/40	2/22	4/11

Table 2 Systemic features and response to sulphapyridine (per patient)

	Overall (n=20)	Successful (n=10)	Unsuccessful (n=6)
Systemic features	14/20	4/10*	5/6*
Skin involvement	5/20	2/10	1/6
Other	9/20	3/10	4/6

*Excludes three patients who developed sulphapyridine allergy and hence had their medication stopped and one patient who had improvement in one eye but worsening in the other.

eyes that were Foster's stage III. Systemic features included lesions involving the skin (five patients), mouth (n=8), pharynx (n=7), nose/sinuses (n=4), and anus/urinary tract (n=2). Seven patients did not have systemic disease. Limbitis was present in six eyes of five patients, filamentary keratitis in one eye, and persistent epithelial defects in two eyes. The overall success was 22/39 (56%) eyes and 10/20 (50%) patients. If the three patients with allergy are excluded, the success rate was 22/33 (67%) eyes and 10/17 (59%) patients.

Those patients who clinically improved with sulphapyridine did so quickly. Mild or no conjunctival inflammation was achieved within 1 month in 14/22 (64%) eyes and by 2 months in the other 8/22 eyes. No patient had an improvement after this period. The follow up of this group was 12.3 (4.0) months and ranged from 7 to 17 months. All patients with objective improvement had a subjective improvement of their ocular surface symptoms and topical steroids were able to be stopped in 4/6 patients. One eye of 22 had progressive cicatrization. This case had shallowing of the lower fornix from 5.0 to 3.5 mm over 10 months despite a lack of inflammation. One patient had objective improvement in one eye but the other remained inflamed. Only 4/10 patients of the successful group had systemic features and of these, three of the four improved with sulphapyridine. This compares with five of six in the unsuccessful group that had systemic features (NS, $p>0.05$). Limbitis

Table 3 Side effects of sulphapyridine

Side effect	Number
Allergy	3/20
Nausea	3/20*
Headache	1/20
Urinary hesitancy	1/20
Mild lymphopenia	1/20

*Two of three resolved after the dose was reduced.

was also associated with a lower response rate; 2/22 successful cases versus 4/11 unsuccessful cases (NS, $p > 0.05$) (Table 1).

The side effects are detailed in Table 3. All cases of allergy presented as a skin rash between 2 and 3 weeks after starting sulphapyridine and required discontinuation of the treatment. By reducing the dose to 500 mg once daily, the nausea resolved completely in two patients and was tolerable in the other. All other patients were maintained on 500 mg twice daily. Two of these patients had a continued therapeutic effect on this dose, the other failed to improve on either dose.

During the study three patients died. Two were still taking sulphapyridine at the time of their death, 10 and 12 months later. The other patient had no improvement from 6 months of treatment and died 4 months after its cessation. These patients were 78, 84, and 84 years old and the causes of death were myocardial infarct, 'died in sleep', and cardiovascular accident respectively.

Discussion

Ocular cicatricial pemphigoid may cause ocular symptoms from many mechanisms. These include ocular surface disease, conjunctival inflammation, keratoconjunctivitis sicca, lid margin disease, entropion, and trichiasis. At any stage, there may be episodes of conjunctival inflammation during which much of the fibrosis occurs.^{2 4 5} With increasing cicatrization the symptoms of ocular morbidity and visual disability become more prominent and this needs to be prevented. Immunosuppressive agents are typically required for 1 year or more.²

The objective of this study was to find an agent that was effective at resolving the ocular inflammation but had fewer short term and long term side effects than existing agents. For moderate to marked ocular inflammation, the current drug of choice is dapsone. In severe inflammation, cyclophosphamide is the most effective although other immunosuppressive drugs may be therapeutic.^{2 3 18 20 21}

Dapsone is a sulphone that inhibits the myeloperoxidase enzyme system of polymorphonuclear leucocytes, suppresses the migration of neutrophils, and stabilises lysosomal membranes.^{22 23} The clinical response is mainly due to inhibition of neutrophil recruitment and function. In OCP, partial or complete improvement of ocular inflammation occurs in 70–71% and is apparent rapidly, 55% within 4 weeks.^{2 24} Over a mean of 35 months, the disease is controlled in 45%. Severe inflammation responds poorly.²⁰ Side effects may be marked, the most significant of which is chronic haemolysis with 95% of patients having a 1.0–3.4 g/dl decrease in haemoglobin.² Other effects include nausea (20%), abdominal pain (10%), peripheral neuropathy (5%), and hepatitis (5%).²

Cyclophosphamide has been successful in treating severely inflamed conjunctiva in OCP but it is particularly toxic.^{2 18} In one ocular series, 100% developed some degree of

anaemia, 83% developed alopecia, 8% developed haematuria, and 8% developed leucopenia.² There is also a long term risk of malignancy.^{25 26}

These drugs contrast with sulphapyridine which has less serious side effects. In this series, the commonest was allergy which prevented its use in 15%. Nausea was present in 15% but this responded to dose reduction. There are no long term risks of malignancy or risks of Stevens-Johnson syndrome.¹⁵ Further, the clinical response was 50–56% and this was apparent promptly. This compares favourably with dapsone.

PHARMACOLOGY OF SULPHAPYRIDINE

Sulphapyridine is a sulphonamide antibiotic with anti-inflammatory properties.²⁷ It is well absorbed orally and has no first pass effect. Elimination is by acetylation which depends on a genetically determined phenotype. The half life of the 'fast acetylators' is 6 hours while that of 'slow acetylators' is 14 hours.²⁸ About 51–81% of patients are slow acetylators.²⁹ This has clinical significance as these patients achieve much higher serum levels for the same oral dose. The anti-inflammatory effects are due to impairment of neutrophils and blood monocytes and inhibition of the cyclooxygenase and lipoxygenase dependent pathways.^{30 31} The effects are reversible³² and similar to some other sulphonamides, such as sulphamethoxypyridazine which is also therapeutic in bullous skin diseases and OCP.^{6 33}

The commonest side effects of sulphapyridine are nausea and headache.³⁴ There can be occasional arthralgia, drug fever, skin rash due to allergy, morphological effects on red blood cells, and mild leucocytopenia.¹⁵ Rarely there is neurotoxicity, hepatotoxicity, polyarteritis, agranulocytosis, blood eosinophilia with pneumonitis, a lupus-like syndrome, and haemorrhagic colitis.³⁵

The main indications have been the inflammatory dermatoses. It is effective in bullous pemphigoid,^{6 36} dermatitis herpetiformis,^{7 37 38} acne conglobata,³⁹ acrodermatitis continua,⁴⁰ erythema elevatum diutinum,⁴¹ necrotising angitis,⁴² pyoderma gangrenosum,⁴³ and subcorneal pustular dermatosis.⁴⁴ These diseases also tend to respond to dapsone. The patients that clinically benefit most from these drugs have significant neutrophil infiltration. This is consistent with the known suppressive effects of sulphapyridine and dapsone on neutrophil function. Sulphapyridine also has a beneficial effect on rheumatoid arthritis, causing both clinical and biochemical improvements.^{8–11} The objectives of treating this disease are similar to those of OCP. In the short term, patients require symptom control. In the long term, permanent tissue damage must be minimised—that is, joint destruction or extensive ocular cicatrization.

ALTERNATIVES TO SULPHAPYRIDINE

Sulphapyridine may not be easy to obtain in some countries. The alternative is sulphasalazine (Salazopyrin, Kabi Pharmacia, Milton Keynes) which has been safely used for

ulcerative colitis for 50 years.¹²⁻¹⁴ Sulphasalazine is cleaved by colonic bacteria into sulphapyridine and 5-ASA.¹⁵ The benefits in colitis are solely due to the 5-ASA which exerts a topical action on the colonic mucosa.²⁷⁻⁴⁵ However, the sulphapyridine is absorbed unaltered and reaches similar levels to the oral administration of the sulphapyridine itself. Two grams of sulphasalazine is the molar equivalent of 800 mg of sulphapyridine.¹⁰ In rheumatoid arthritis, oral administration of sulphasalazine or sulphapyridine results in the same beneficial anti-inflammatory response.¹⁰ Therefore, sulphasalazine could be substituted for sulphapyridine in OCP.

LONG TERM OUTCOME

The follow up for this series is 12.3 months for which there is a success rate of 50–56%. All 'successful' patients had a reduction of conjunctival inflammation and symptomatic improvement. This compares with dapsone where 70% may respond initially although only 45% have a sustained response over 35 months.²⁰ With sulphapyridine, there has been minimal progression of the cicatrization over 12 months (1/22 eyes) although the longer term outcome is not known.

Sulphapyridine has been shown to be safe, effective, and have minimum side effects in OCP. Its role is mainly in moderate and marked conjunctival inflammation unresponsive to topical treatment. Allergy may prevent long term treatment in 15% and it may be less effective in treating limbitis and in those patients with systemic features.

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