The effect of disodium cromoglycate and ketotifen on the excretion of histamine and N^τ-methylimidazole acetic acid in urine of patients with mastocytosis

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Treatment of four mastocytosis patients with the mast cell stabilising drugs, disodium cromoglycate and ketotifen failed to alter significantly the urinary excretion levels of histamine or N^τ-methylimidazole acetic acid. No clinical improvement was noted in any subject after treatment by either drug.

Keywords mastocytosis histamine N^τ-methylimidazole acetic acid sodium cromoglycate ketotifen

Introduction

Dermatoses which involve excessive or abnormal release of mast cell products are frequently treated by systemic administration of H₁-antihistamines. However these are usually only partially effective. One reason for this may be the involvement of other mast cell products including platelet activating factor (PAF), prostaglandin D₂ (PGD₂) and proteases (Gramdel *et al.*, 1985; Heavey *et al.*, 1986; Roberts *et al.*, 1980; Schwartz *et al.*, 1987). In the absence of precise identification of non-histamine mast cell-derived mediators, any attempt to prevent degranulation of mast cells and to inhibit secretion or release of their pro-inflammatory products, seems logical.

Disodium cromoglycate, a mast cell stabilising compound, has been shown to be effective in control of symptoms and signs in patients with systemic mastocytosis (Soter *et al.*, 1979). Oral administration caused reduction in both systemic and cutaneous manifestations. Whether these effects were indirect, via an action on intestinal mast cells, or systemic, is uncertain. Ketotifen, as well as being a histamine H₁-receptor antagonist, prevents mediator release from mast cells (Craps & Ney, 1977). Ketotifen has been used successfully in cold urticaria, oral administration

causing both reduction in clinical severity and inhibition of cold evoked histamine release (Huston *et al.*, 1986).

The measurement of histamine in man is complicated by the variety of exogenous sources for this molecule and by difficulties with the assay, especially of histamine in urine. In this study we have observed the effect of both disodium cromoglycate and ketotifen given orally, at different occasions, on the symptoms and signs in mastocytosis. Urinary histamine and the major endogenous metabolite, N^τ-methylimidazole acetic acid (MIAA) were measured using specific gas chromatography-mass spectrometry (GC-MS) assays.

Methods

Patients

Four patients (three males) aged 33–61 years, who had given informed consent for the investigation, were studied. Two of these had evidence of systemic involvement. None of these patients had responded satisfactorily to antihistamine treatment.

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Patient A This 54 year old female had extensive lesions of urticaria pigmentation for 16 years. Wealing was noticed only after a hot bath and the rash was not improved by a course of photochemotherapy (8-methoxy psoralen UV-A). There were no systemic symptoms. Bone marrow examination revealed increased numbers of mast cells.

Patient B A 34 year old man presented with a pigmented eruption with widespread distribution for the last 7 years. Wealing was minimal and occurred mainly after a bath. Neither antihistamines, nor a course of UV-B, had relieved his symptoms. The diagnosis was confirmed histologically on a skin biopsy. Bone marrow trephine and abdominal ultrasound examinations yielded negative results and there was no evidence of systemic involvement.

Patient C A 63 year old male had an histologically confirmed, progressively spreading, pigmented eruption for 18 years. He had no systemic symptoms attributable to his mastocytosis and only mild wealing. His abdominal ultrasound and radiological skeletal survey examinations were normal. He was poorly responsive to antihistamine treatment.

Patient D A 47 year old male had widespread urticaria pigmentosa for 15 years. Bone marrow aspiration showed extensive infiltration by mastocytosis and there were radiological deposits in the skull vault, pelvis and long bones. There was troublesome pruritus, but the main symptom was persistent backache which was attributed to involvement of the spine by mastocytosis.

Drug treatment

Disodium cromoglycate (Nalcrom, Fisons PLC) was administered in dosage 200 mg four times daily, after meals, for 2 weeks, and ketotifen was given in dosage 2 mg, twice daily, orally, after meals for 2 weeks. The two courses were separated by an interval of at least 3 weeks. Throughout the experimental periods the patients were asked to avoid foodstuffs with a high histamine content. One patient (patient C) withdrew from the ketotifen leg of the study.

Clinical assessment

This was carried out at the beginning and the end of the 2 week period. The degree of pruritus over the proceeding 24 h was graded using a 10 cm visual analogue scale and the width of a weal 2

min after elicitation on the upper back, using a dermatographometer set at constant pressure, was measured (James & Warin, 1969).

Pharmacological studies

24 h urine samples were collected prior to administration of each drug and a second 24 h urine sample was collected at the end of the 2 week course of treatment. The total volume of each sample was recorded and an aliquot was analysed for the creatinine content.

Histamine was extracted and analysed by GC-MS as its tris-pentafluorobenzyl derivative, after addition of the deuterated internal standard $\alpha, \alpha, \beta, \beta$ -[^2H] $_4$ -histamine (Merck Isotopes Ltd., Montreal, Canada) as described by Roberts *et al.* (1985). MIAA was measured after addition of N^+ -[C^2H_3]-methylimidazole acetic acid as internal standard, by GC-MS on the octafluoropentyl ester, heptafluorobutyl derivative (Mallet & Rendell 1988).

Results

The results for individual patients are given in Figure 1 and the summarised results in Table 1. Patients A and D with clinical evidence of systemic involvement had raised levels of histamine and MIAA in the urine, although pre-ketotifen treatment levels for histamine in patient D were within normal range. However neither of these two patients nor the two who had no clinical evidence of systemic involvement or elevated levels of MIAA, showed any reduction in urinary excretion of the amines following 2 weeks' treatment by either oral DSCG or ketotifen.

No clinical benefit was observed with either drug.

Discussion

Our results contrast with those of Soter (1979) who described marked symptomatic benefit in patients with systemic mastocytosis treated with oral DSCG, after a 2-3 week delay period. Furthermore Huston *et al.* (1986) have reported reduction of cold-evoked histamine levels in venous blood draining the cold challenged arm of patients with cold urticaria following oral ketotifen treatment. Our results are in agreement with those of Frieri *et al.* (1985) who found no change in urinary histamine concentration in mastocytosis patients treated with DSCG. Although, in our studies, ketotifen was ineffective in lowering urinary histamine and MIAA levels,

Figure 1 Effect of 2 weeks' oral administration of DSCG or ketotifen on urinary excretion of histamine (panel a) and its major metabolite (*N*⁷-methylimidazole acetic acid (panel b), in four patients (A,B,C,D) with mastocytosis. Open triangles represent pre-treatment values and closed triangles represent post-treatment values. Solid lines represent limits of normal range for each measurement.

Table 1 Histamine and MIAA concentrations in urine before and after treatment with DSCG or ketotifen.

	Pre	Post		Pre	Post
A. <i>Histamine</i> *			<i>MIAA</i> **		
Mean	0.137	0.159	Mean	4.55	8.53
s.e.mean (n=4)	±0.051	±0.064	s.e.mean (n=4)	±2.48	±6.32
B. <i>Histamine</i>			<i>MIAA</i>		
Mean	0.051	0.047	Mean	6.89	8.63
s.e.mean (n=3)	±0.018	±0.021	s.e.mean (n=3)	±2.38	±3.63

* $\mu\text{mol mol}^{-1}$ creatinine, ** mmol mol^{-1} creatinine.

A = results after treatment with DSCG.

B = results after treatment with ketotifen.

it is conceivable that histamine release from mast cells of mastocytosis patients may be regulated differently when compared with cells of patients with physical urticarias.

Roberts *et al.* (1985) have discussed the errors inherent in published radioenzyme assays for histamine, especially when these are applied to urinary extracts and they have compared them to a GC-MS method. We chose to use GC-MS methods for both histamine and MIAA. In man approximately 60% of the total excreted histamine is present in urine as MIAA and this is reported to reflect more closely endogenous his-

tamine turnover, since it is less influenced by dietary or microbiological sources.

Systemic mastocytosis is characterised by the presence of unusually high population densities of mast cells in the skin and internal organs. Treatment by oral histamine antagonists or putative mast cell stabilising drugs appears to have little clinical or pharmacological suppressive activity towards this disease.

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