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REPORTS

Decreased Urinary Histamine Metabolite after Successful PUVA Treatment of Urticaria Pigmentosa

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The effect of PUVA therapy on pruritus, the skin mast cell population and histamine metabolism has been studied in 3 patients with urticaria pigmentosa and manifestations of systemic mastocytosis. Relief of itch was found concomitant with a significant decrease of the major histamine metabolite 1-methyl-4-imidazoleacetic acid in the urine. The decrease occurred during the first 2 mo after starting PUVA therapy and was sustained during an observation period of 3 mo after discontinuation of the treatment. At this time a reduction of the number of mast cells was found in skin biopsy specimens. No evidence of acute histamine release in association with PUVA treatment was obtained. These results suggest that this effective new treatment for urticaria pigmentosa reduces the histamine turnover in the skin by inhibiting mast cell proliferation.

Urticaria pigmentosa (UP) is a dermal proliferation and accumulation of mast cells while systemic mastocytosis implies an infiltration of noncutaneous tissues as well. The lesions of UP may be either solitary or generalized. Pruritus is a disabling symptom of the disease, which often presents with urtication, dermographism and flushing. Treatment with corticosteroids, antihistamines and histamine liberators only occasionally relieves pruritus.

A recent report by Christophers' et al [1] described regression of the disabling pruritus of UP after treatment with 8-methoxypsoralen and UVA-light (PUVA). The underlying mechanism for the apparent effect of this new therapy is not known. In this study we are able to confirm Christophers' et al [1] encouraging results but also report a substantial decrease of 1-methyl-4-imidazoleacetic acid (MeImAA), the major histamine metabolite in the urine, about 2 mo after starting PUVA therapy. As MeImAA is exclusively derived from histamine and accounts for 70–80% of the total amount of histamine metabolized in the body [2], this study offered a possibility to relate histamine turnover to the different systemic manifestations of mastocytosis and to the effect of PUVA treatment on the number of mast cells in the skin.

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Abbreviations:
MeImAA: 1-methyl-4-imidazoleacetic acid
UP: urticaria pigmentosa

PATIENTS AND METHODS

Three adult patients with well-known UP since many years were studied. The diagnosis was confirmed clinically and by skin histology. Further investigations of the patients revealed systemic mastocytosis as shown by ^{99}Tc bone scan, sternal puncture and liver scintigraphy. Relevant clinical details and the course after treatment are summarized in the Table. The patients received 0.5 mg of 8-methoxypsoralen per kg body weight 2 hr before UVA treatment (PUVA 4000, Waldmann, Germany). The initial UVA dose of 1 J/cm^2 was adjusted to the minimal phototoxic dose, which was maintained all through the treatment period. The final dose was 5 J/cm^2 for GS, 15 J/cm^2 for LS and 6 J/cm^2 for EG. The accumulated dose for the 3 patients studied is given in the Table. GS was treated twice a week for 34 weeks while PUVA was given twice a week for 10 weeks in LS and for 18 weeks in EG, thereafter these patients received their treatment once a week for 11 and 14 weeks respectively. In all 3 patients PUVA treatment was then discontinued during the summer.

Skin Histology

Biopsy specimens were obtained from hyperpigmented patches of the thoracic skin before and 10–12 weeks after interrupting PUVA therapy. 4-mm cutaneous punch biopsies were procured. For anaesthesia 1% xylocaine with adrenaline was injected in the periphery of the area to be biopsied. Embedding was performed in paraffin and 2–3 μm thick sections were stained with Giemsa's reagent.

Urine was collected from 8 AM in 24 hr periods and usually on 2 consecutive days, during PUVA therapy on the day of PUVA treatment and on the day before. The PUVA therapy was given between 8 and 12 AM. To avoid bacterial growth, the urine was acidified with hydrochloric acid to a pH of less than 2. During the days of study the patients ate a standardized diet with a defined, low histamine content [2].

Histamine in urine was determined with the enzymatic double isotope method described by Beaven, Jacobsen, and Horakova [3] as modified by Aadland, Berstad, and Granerus [4].

1-methyl-4-imidazoleacetic acid (MeImAA) was converted to the ethyl ester, which was extracted with ether and estimated by thin-layer chromatography according to the method of Granerus and Magnusson [5], with slight modifications [6]. The variability between excretion values from consecutive days was determined according to the formula $\sqrt{\sum d^2/2n}$ and found to be 1.61 mg/24 hr, corresponding to a coefficient of variation of 16%, which is in the same order as reported earlier in patients with polycythemia vera [7].

In Fig 1 urinary levels of MeImAA are expressed in terms of individual mean creatinine excretion to correct for variable urine collection.

RESULTS

Regression of the itch was observed within 2 weeks after starting PUVA therapy and all the patients were symptomless after 3–6 weeks. The hyperpigmented maculae of UP seemed to fade during treatment in all patients but did not disappear. Any change in the systemic manifestations of mastocytosis was not possible to measure.

The 3 patients differed markedly regarding the urinary excretion of MeImAA. Before PUVA treatment there was a large increase in GS, a moderate increase in LS and a slight increase

Clinical details of the 3 mastocytosis patients studied

Patient/ sex	Age (yr)		Manifestation of mastocytosis	Pruritus			Total UVA dose (J/cm²)
	Present	At onset		At onset	PUVA 2 mo	3 mo after PUVA	
GS/F	70	51	Hepato-splenomegaly and bone scan abnormalities	Severe	Symptomless	Mild	148
LS/M	49	42	Bone marrow infiltration	Moderate	Symptomless	Symptomless	278
EG/M	52	33	Bone scan abnormalities	Mild	Symptomless	Symptomless	184

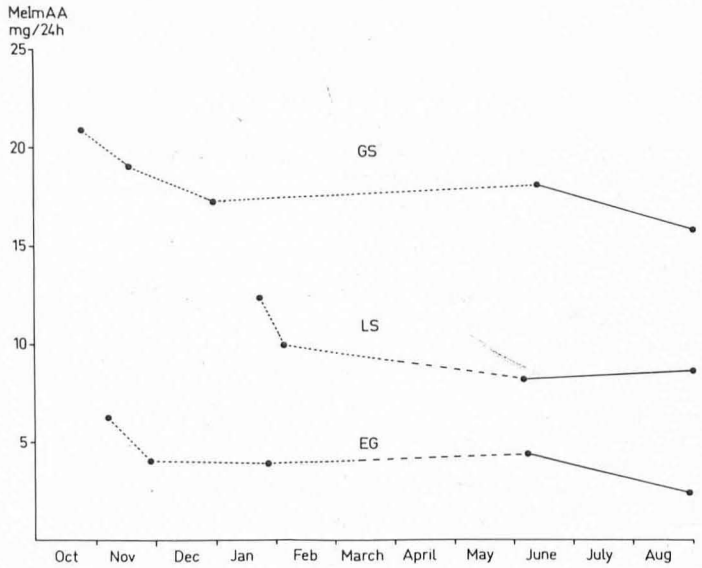

FIG 1. Urinary excretion of the histamine metabolite methylimidazoleacetic acid (*MeImAA*) in 3 mastocytosis patients immediately before, during and after PUVA treatment. *Dotted line:* PUVA twice a week. *Dashed line:* PUVA once a week. *Solid line:* No treatment. Each value represents the mean excretion of 2 consecutive days after correction for varying creatinine excretion.

in EG compared to normal controls [2] and other patients with mastocytosis [8]. In all 3 patients a significant (paired *t*-test) decrease in MeImAA excretion occurred within the first 2 mo of therapy, amounting to 2–4 mg/24 hr, whereafter the urinary excretion of MeImAA remained at about the same level (Fig 1). Three months after PUVA treatment had been stopped the excretion of MeImAA in the urine was not significantly changed but patient GS had a mild pruritus while the others were still free from symptoms.

Urinary histamine was measured on altogether 54 occasions but, owing to the large intraindividual scatter, there was no evident decrease during therapy in any of the patients. The mean levels of histamine in the urine were 79 in patient GS (range 43–134), 79 in patient LS (range 50–199) and 29 μg/24 hr in patient EG (range 13–46). A significant correlation between histamine and MeImAA in the urine existed in the total material (r 0.58, $p < 0.01$, n 28).

In order to detect an acute histamine release during PUVA therapy urine was collected the day before treatment and 1–3 days after treatment. There was no significant increase in either histamine or MeImAA excretion during the day of PUVA treatment compared to the day before, neither was there any increase in histamine excretion during the second and third day after PUVA. However, in patient GS increased pruritus was noticed for a few hours after the first 4 doses of psoralen and UVA-light irradiation. The other 2 patients never experienced any acute symptoms.

An abundance of mast cells were seen in the histology sections before PUVA therapy in patients GS and LS, while only a few mast cells could be seen 10–12 weeks after therapy (Fig 2), the number being considered not different from what is found in normal skin.

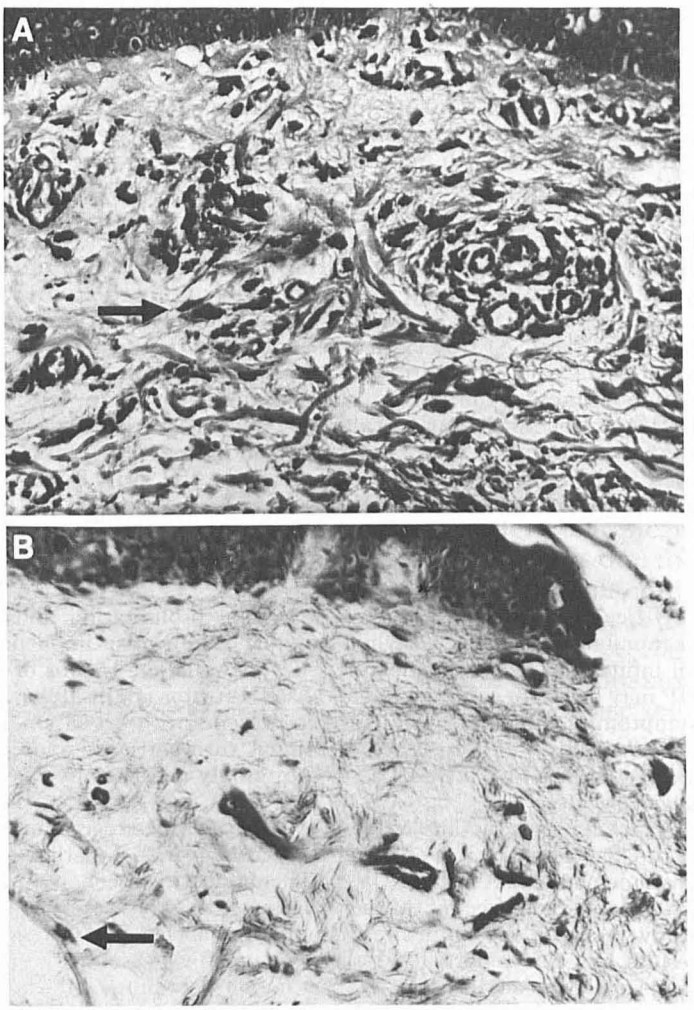

FIG 2. Mast cell density of lesional skin in patient GS before (*A*) and 3 mo after PUVA therapy (*B*). *Arrows* point at typical mast cells (Giemsa's reagent, reduced from × 150.)

DISCUSSION

The results of this study show a decrease in the urinary excretion of the main histamine metabolite MeImAA during the first 2 months after starting PUVA therapy. The decrease occurred concomitantly with the clinical improvement. The treatment did not result in any complication typical of acute histamine release, such as headache, dizziness or hypotension. The potential risks of shock were, however, considered in connection with the decision to use small PUVA doses initially. There was no indication of histamine release associated with the treatment, as studied up to 72 hr after exposure to PUVA. Previously, one patient with extensive cold urticaria has been investigated before and during attacks [9]. In this patient the

urinary excretion of histamine and MeImAA increased about four times during days of symptoms, showing the usefulness of these analyses for detection of acute histamine release.

MeImAA is the major histamine metabolite in the urine of normal subjects and also in patients with mastocytosis, as shown by injection of ^{14}C-histamine in two patients [8] and ^{14}C-histidine in one patient [10] and analysis of labeled histamine and metabolites in the urine. Under steady-state conditions, i.e., without symptoms of acute histamine release, most patients with UP studied in our laboratory who excreted abnormal amounts of MeImAA were found to have systemic manifestations of their disease [8]. This was also true for the patients in this study who had mast cell infiltrations in the skeleton, in the bone marrow and in the liver. We believe that the urinary excretion of MeImAA, as being the major histamine metabolite, is likely to reflect the total mast cell population of the mastocytosis patient. In one patient with generalized mastocytosis it has been possible to measure the mean histamine turnover time and calculate the total histamine pool of the body [10]. The pool was found to be 700 mg with a turnover rate of around 30 mg histamine per day. This strongly supports the hypothesis that mastocytosis patients with increased amounts of histamine metabolites in the urine have an increased histamine pool, corresponding to the mast cell proliferation in the tissues. Furthermore, in the present study the MeImAA-excretion in 2 of the patients decreased but was not normalized, in spite of a normalized number of mast cells in the skin, which is consistent with a generalized mastocytosis in these patients and indicates a substantial histamine pool in other organs than the skin.

Theoretically, a decreased urinary MeImAA after PUVA might be due to either a decreased histamine pool in the body or a prolonged histamine turnover time. The histological finding of a reduction of the number of mast cells in the skin after treatment clearly indicates a decrease of the skin histamine pool. This interpretation is also in accordance with the generally accepted photobiological effects produced by psoralens, namely a photoconjugation to the pyrimidine bases of DNA, which has a marked inhibitory effect of DNA synthesis [11] and cell division [12]. It is also possible that PUVA treatment causes an impaired histamine synthesis in the mast cells, but the fact that the interruption of PUVA treatment for 3 mo did not seem to replenish the histamine stores and increase MeImAA excretion is in accordance with a reduced mast cell population.

Thus, the beneficial effect of PUVA in these UP patients seems to be associated with a diminished histamine turnover in the skin secondary to a reduced number of mast cells. However, the results do not prove that histamine is a causative factor of the pruritus in these patients. Indeed, it is common clinical experience that antihistamines seldom relieve the itch of UP. The new H_2-histamine antagonist cimetidine was also given to patient GS for several weeks without any effect on the pruritus. However, it must be remembered that the histamine concentrations in the skin of UP patients might be high in close vicinity of the receptors eliciting the itch, so that the usual dose of antihistamines are ineffective. It was recently reported that oral administration of the antiallergic drug disodium cromoglycate produced marked amelioration of pruritus and other symptoms in systemic mastocytosis [13]. This was achieved without any change in urinary histamine excretion and the authors concluded that disodium cromoglycate may act by mechanisms other than stabilization of mast cell membranes, but, as shown in this study, urinary histamine may not be a reliable indicator of changes in histamine turnover in mastocytosis patients.

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