Increased plasma histamine levels in uraemic pruritus

FELIX STOCKENHUBER, ROBERT W. KURZ*, KASPAR SERTL, GEORG GRIMM AND PETER BALCKE

Department for Renal Disease and Haemodialysis, Vienna University School of Medicine, Vienna, and *First Medical Department, Kaiser Franz Josef Hospital, Vienna, Austria.

(Received 30 January/17 April 1990; accepted 5 June 1990)

SUMMARY

1. We determined plasma levels of histamine in uraemic patients and examined their correlation with the presence of pruritus.
2. In 27 patients with chronic renal failure, plasma histamine levels were analysed by radioimmunoassay and were compared with those of 40 healthy adult subjects. The control population showed plasma histamine concentrations of 185 ± 33 pg/ml, which were significantly lower than those of the patients with renal insufficiency. The highest levels (552 ± 116 pg of histamine/ml) were found in 16 patients with chronic renal failure (mean serum creatinine 5.1 ± 1.0 mg/dl) and severe itching.
3. Twelve patients with pronounced pruritus who were on maintenance haemodialysis (serum creatinine 9.2 ± 1.2 mg/dl) had a mean plasma histamine concentration of 515 ± 81 pg/ml. Fifteen patients on regular haemodialysis (serum creatinine 9.0 ± 1.5 mg/dl) and who experienced itching had plasma histamine levels (322 ± 40 pg/ml) which were significantly lower (P < 0.01) than those of the patients with pruritus but which were elevated compared with those of the control population (P < 0.01).
4. No correlation could be found between increased plasma histamine levels and the type of dialysis membrane used or the method of sterilization of the membrane.
5. Haemodialysis alone did not reduce plasma histamine concentrations, although high concentrations could be detected in the ultrafiltrate. In six patients a rapid decrease in plasma histamine concentration from 565 ± 134 pg/ml to within the normal range could be detected after 60 min of combined haemodialysis and haemoperfusion.
6. Our results show that increased plasma levels of histamine are found in patients with renal insufficiency and pruritus, and we conclude that this mediator might be involved in the genesis of uraemic pruritus.

Key words: chronic renal failure, haemodialysis, histamine, pruritus, uraemia.

INTRODUCTION

Moderate to severe itching is a frequent symptom of uraemia that affects as many as 86% of patients [1-4]. The pathogenesis of uraemic pruritus remains to be clarified. Various possible explanations, such as xerosis of the skin, derangement of sweating, secondary hyperparathyroidism and cutaneous mast cell proliferation, have been suggested [5-8]. The lack of understanding of the underlying mechanism has led to various therapeutic approaches which have proved helpful only in rare cases. Histamine is known as a potent inducer of pruritus in various diseases and might be involved as a mediator of uraemic itch as well. It is released from basophilic polymorphonuclear leucocytes and mast cells which are found to be increased in the skin and other organs of uraemic patients [9-12]. Thus histamine has been suggested as a causative factor in uraemic pruritus, but its mediating role has never been elucidated and has remained under investigation. In addition, a therapeutic approach to uraemic pruritus with antihistamines is unsatisfying in most cases. In the present study we determined the plasma histamine levels in patients with uraemic pruritus and evaluated a putative correlation between uraemic pruritus and increased plasma histamine levels [9-12].

METHODS

Patients and dialysis

The study population comprised 27 adult patients (15 males, 12 females) with chronic renal failure. Their mean serum creatinine concentration was 5.1 ± 1.0 mg/dl and their mean age was 46 years (range 22-63 years).
Sixteen patients in this group suffered from pronounced itching (group I). The classification of pronounced or severe pruritus was assessed only in patients exhibiting all of the following criteria: complaints about pronounced or severe pruritus, telltale signs of scratching such as excoriations, haemorrhagic crusts and lichenifications, and local and systemic use of antihistaminic agents. Group II comprised the remaining 11 patients with chronic renal failure and no pruritus. Since pruritus has also a psychological aspect, in this group were also included patients who complained sporadically about mild itching but had never exhibited the objective signs of pruritus mentioned above.

An additional 27 patients with end-stage renal disease undergoing maintenance haemodialysis were enrolled in the study. Twelve of them complained of severe pruritus (group III). The same criteria for severe pruritus were applied as in group I. Their ages ranged from 27 to 58 years with a mean of 42 years. They received regular haemodialysis for a mean period of 43 months (range 32–51 months). Their serum creatinine concentration was 9.2 ± 1.2 mg/dl. The remaining 15 patients were free from pruritus and were aged from 23 to 61 years with a mean of 44 years (group IV). They had been on regular haemodialysis for an average of 16 months (range 4–22 months) and had a serum creatinine concentration of 9.0 ± 1.5 mg/dl.

Haemodialysis was performed three times a week for 4 h each time. In all patients a dialyser with a Cuprophan fiber membrane sterilized with ethylene oxide was used (Gambro Fiber GFS 120 H; Gambro, Hechingen, Sweden). In order to exclude major influences of differences in the clearance rate, the biocompatibility of the membrane and the sterilization method, in the second part of the study the type of dialyser was changed, using alternatively in all patients dialysers with a synthetic Polysulphon membrane sterilized with ethylene oxide (Fresenius Hemoflow F 6; Fresenius AG, Bad Homburg, F.R.G.) and a Cuprophan membrane sterilized by γ-irradiation (Secon 122; Secon, Göttingen, F.R.G.). The study period for each dialyser was 4 weeks. Plasma histamine levels in each group were compared at the end of each period.

In six patients haemoperfusion was performed. For the haemoperfusion procedure a cartrige of cellulose-coated activated charcoal was used (Adsorba 300 C; Gambro, Hechingen, Sweden).

All medications were continued. None of the patients had a history of pruritus or any dermatological disease antedating renal failure. Patients with systemic disease such as diabetes mellitus or collagen disease were excluded from the investigation.

Forty healthy probands without any history or symptoms of allergy served as controls. Their ages ranged from 25 to 56 years with a mean of 41 years.

Assays

Histamine concentrations in plasma samples were quantitatively analysed by a novel, commercially available radioimmunoassay (Immunootech, Marseille, France). This immunoanalysis of histamine is performed by competition between modified histamine in the sample and the iodinated histamine tracer for binding to the monoclonal antibody coated on the tubes. Because of the small size of this amine, histamine was coupled to a carrier via a chemical linkage before immunization. In order to increase histamine recognition by antibodies, the same chemical modification (acylation) has to be reproduced on samples and tracer. An acylating reagent, H-hydroxy-succinimide-succinyl-glycinamide, was designed especially for the acylation of histamine in biological samples. The combination of sample acylation and the use of monoclonal antibodies led to a highly sensitive and specific technique for the determination of histamine [13, 14]. The details of this assay are described elsewhere [13, 14]. Non-specific binding of tracer in our laboratory was 0.5% of the radioligand added. The sensitivity of the assay was 10 pg/ml. Recoveries of histamine from plasma samples spiked with various amounts of acylated histamine ranged, even in uraemic plasma, from 85 to 94%. Within- and between-assay precisions were 5% and 11%, respectively. Each sample was assayed in triplicate. The addition of histaminase reduced even very high histamine levels to zero. In order to exclude an influence of antihistamines or their metabolites on the histamine assay five patients on haemodialysis without pruritus ingested 20 mg of the antihistamine Astemizol (Hismanal; Janssen and Cilag Pharma, Vienna, Austria) daily for 1 week. As this trial revealed normal histamine concentrations any influences of antihistamines on the assay could be excluded. Before starting the dialysis procedure blood samples were drawn from an antecubital vein into ethylenediaminetetra-acetate-coated glass tubes and immediately centrifuged (300 g) at 4°C. Aliquots of the upper two-thirds of the plasma were stored at −70°C. The histamine assay was carried out by an investigator who was blind to the clinical status of the patients. Pruritus was assessed by an investigator who was blind to the results of the histamine assay during the study period.

Parathormone was measured by a commercially available radioimmunoassay kit (Diagnostic Systems, Laboratory Inc., Webster, TX, U.S.A.).

Serum calcium, phosphate, magnesium and creatinine concentrations and blood urea nitrogen were measured by autoanalyzer (Du Pont, Bad Neuheim, F.R.G.) and serum ferritin was determined by an immunoradiometric assay (Becton Dickinson, Cowley, Oxon, U.K.).

**Statistical analysis**

Statistical analysis was performed by analysis of variance among the groups. The level of significance was set at *P*<0.05. All values are expressed as means ± s.d.

**RESULTS**

The mean plasma histamine concentration in the healthy control subjects was 185 ± 33 pg/ml. The highest plasma levels of histamine (552 ± 116 pg/ml) were found in patients with chronic renal failure, who were not on
regular haemodialysis but suffered from pronounced pruritus at the time of investigation (group II). The 11 patients with chronic renal failure without itching (group III) had significantly lower plasma histamine concentrations (344 ± 37 pg/ml; P<0.01). Plasma histamine levels were significantly elevated in 12 patients on regular haemodialysis who complained about severe pruritus (group I). They had a mean plasma histamine concentration of 515 ± 81 pg/ml. In the 15 patients on haemodialysis who had no itching (group IV) plasma histamine levels were lower than in group III, but were significantly increased (322 ± 40 pg/ml, P<0.01) (see Fig. 1) in comparison with normal control subjects. Patients with chronic renal insufficiency and severe pruritus showed significantly higher plasma histamine levels compared with patients without itching (P<0.01) as well as compared with healthy control subjects (P<0.001) irrespective of whether they were on haemodialysis or not. Although the patients on regular haemodialysis who did not have pruritus showed significantly lower levels compared with patients suffering from itching (P<0.01), their mean plasma histamine concentration was still significantly higher than that of the healthy control subjects (P<0.01).

Increased plasma levels were independent of the method of sterilization or the type of material of the membrane, as the trial using different kinds of dialysers in a rotating schedule showed no significant variation in the individual plasma histamine levels. In the group with severe pruritus mean plasma histamine levels were 515 ± 81 pg/ml using the Cuprophan dialyser sterilized with ethyleneoxide, 503 ± 97 pg/ml at the end of the treatment period of 4 weeks with the Polysulphon dialyser and 510 ± 79 pg/ml at the end of the treatment period with the Cuprophan dialyser sterilized by γ-irradiation. The corresponding values in the chronic haemodialysis patients without pruritus were 322 ± 40, 316 ± 45 and 327 ± 47 pg/ml, respectively.

In 17 patients we measured histamine concentrations before and after haemodialysis (see Fig. 2). The concentration before and after haemodialysis showed a slight increase but the values did not differ significantly.

In eight patients histamine was measured in the ultrafiltrate and exhibited similar concentrations in five patients and even higher concentrations in three patients compared with the concentrations in plasma (see Fig. 3).

In six patients haemodialysis was combined with haemoperfusion for one session. During this procedure plasma histamine concentrations rapidly decreased from 565 ± 134 pg/ml to normal values. This reduction was accompanied by an instant disappearance of pruritus (see Fig. 4). The gradual recurrence of itching within 1–2 weeks after the haemoperfusion procedure was correlated with a protracted increase in histamine within this time. The mean plasma histamine levels of these six patients increased from a below normal value of 48 ± 27 pg/ml 20 min after the end of haemoperfusion to 138 ± 39 pg/ml (P<0.01) within 24 h, and to 228 ± 48 pg/ml, 265 ± 59 pg/ml, 307 ± 64 pg/ml and 358 ± 72 pg/ml, respectively, on days 3, 5, 7 and 9 after the haemoperfusion procedure.

The serum concentration of parathormone was found to be elevated in all patients on regular haemodialysis (10.3 ± 2.5 ng/ml in group III compared with 9.8 ± 3.2 ng/ml in group IV) but no significant difference could be detected between patients with and without pruritus.

Serum calcium, phosphate, magnesium and ferritin concentrations and blood urea nitrogen in the various groups are shown in Table 1. There were no significant differences in any of these parameters between the corresponding groups with and without pruritus (group I compared with group II, group III compared with group IV).

![Fig. 1. Plasma histamine concentration in the patients studied. Mean plasma histamine levels were significantly elevated in group I and III (**P<0.001) in comparison with normal subjects (the normal range was established by measuring plasma histamine levels in 40 healthy subjects). Mean plasma histamine levels in group II and IV were significantly elevated in comparison with normal control subjects (*P<0.01), but were significantly lower in comparison with groups I and III (P<0.01). Bars represent median values.

DISCUSSION

Severe and persistent pruritus is one of the most disturbing but poorly understood symptoms of uraemia, with a reported prevalence of up to 86% [1–4]. The underlying cause of the itching is unknown, but several factors have been implicated. Xerotic and hypohydrotic skin due to atrophy of sebaceous and sweat glands, as well as disturbances of calcium and phosphorus metabolism, in uraemia
Fig. 2. Plasma histamine concentrations in 17 patients immediately before and after 4 h of haemodialysis treatment. Concentrations after haemodialysis were not significantly different when compared with concentrations before haemodialysis.

Fig. 3. Histamine concentrations for eight patients in plasma and in the ultrafiltrate. Concentrations in the ultrafiltrate were not significantly different from those in serum.

Fig. 4. Time course of the decline in plasma histamine concentrations in six patients in whom haemodialysis was combined with haemoperfusion.

Histamine is generally regarded as a potent pruritic mediator in urticaria and it evokes a pruritic sensation if injected into skin. It is attractive to speculate that raised serum histamine levels correlate with the severity of uraemic pruritus [9], but this concept has not been proven up to now. Our results showed a significantly higher plasma concentration of histamine in chronic renal failure patients compared with healthy control subjects. Furthermore, a particular plasma concentration of histamine corresponded with the occurrence of pruritus. There seems to be a threshold for the plasma histamine concentration in a suitable environment predisposing to itching above which one perceives pruritus. Increased plasma histamine levels might be a consequence of enhanced synthesis and release of histamine by an augmented number of mast cells. Mast cell proliferation has been found in the skin and other organs of a high percentage of uraemic patients. This may represent a reactive response to several stimuli present in uraemia [9, 26]. In accord with this, Matsumoto et al. [10] found increased numbers of mast cells in the skin of patients undergoing maintenance haemodialysis. Most uraemic patients show some degree of hyperparathyroidism, and high concentrations of parathormone were shown to induce mast cell proliferation in rats [26]. Moreover, parathyroidectomy has resulted in remission of uraemic pruritus [16, 25]. Since histamine and its metabolites are normally excreted in the urine, the retention of histamine in renal insufficiency might contribute to elevated plasma levels as well.

Histamine, due to its low molecular mass (111 Da), is removed by haemodialysis and it is found in the ultrafiltrate. Surprisingly, we could not detect a significant decrease in plasma levels of histamine, despite remarkable titres in the ultrafiltrate indicating an efficient elimination. In eight patients histamine concentrations were measured in the ultrafiltrate and were found to be even higher than the plasma concentration in two cases. This might be a consequence of pronounced histamine liberation from mast cells and basophilic polymorphonuclear leucocytes during extracorporal circulation.

Complement activation during haemodialysis is a well-known phenomenon [27]. Some products of complement activation, namely C3a, C4a and C5a, induce several
biological responses, such as leucocaggregation and histamine release from mast cells and basophilic granulocytes, which may contribute to adverse clinical and biochemical changes [28, 29]. Thus increased histamine liberation during haemodialysis might be due to complement activation during haemodialysis. However, we believe that complement activation does not play a major role in histamine formation, since our rotating schedule with different types of membranes leading to high (Cuprophan) or low (Poly-sulphon) grade activation [30, 31] did not cause statistically significant variations in the individual histamine levels. Moreover, the lack of variation in the histamine levels suggests that potential differences in the clearance rate of histamine between the different kinds of dialysers commonly used are negligible. Similarly, major influences of the method of sterilization of the dialyser can be excluded.

An efficient decrease in plasma histamine levels was achieved by combining haemodialysis with haemoperfusion. Haemoperfusion is a process whereby blood is passed through a cartridge packed with activated charcoal or carbon, which bind many substances such as drugs and endogenous compounds which are not or insufficiently removed by haemodialysis [32]. This procedure was performed in six patients, whose plasma histamine concentration fell from 565 ± 134 pg/ml to within the normal range within 1 h of haemoperfusion and was accompanied by an instant cessation of itching. This might be an explanation for the instant cessation of pruritus during haemodialysis treatment with simultaneous haemoperfusion and could underscore a mediating role for histamine. Some authors have reported that sunburn-spectrum ultraviolet (u.v.-B) phototherapy reduces the severity of uraemic pruritus [21, 23]. It had been suggested that u.v.-B light inactivates circulating substances such as histamine, vitamin A or other mediators present in uraemia [23, 33]. It would be worthwhile investigating possible changes in histamine concentrations during phototherapy in order to obtain further information about the mechanism of this therapeutic approach.

We are aware that several other factors present in uraemic patients create a suitable environment predisposing to itching. Nevertheless our findings could indicate a key role for increased plasma levels of histamine and justify further evaluation of the pathogenetic role of histamine in uraemic pruritus.

Table 1. Serum concentrations of calcium, phosphate, magnesium and ferritin and blood urea nitrogen in the patients studied

<table>
<thead>
<tr>
<th>Group I (n = 16)</th>
<th>Group II (n = 11)</th>
<th>Group III (n = 12)</th>
<th>Group IV (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.2 ± 0.3</td>
<td>2.1 ± 0.4</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>Serum phosphate (mmol/l)</td>
<td>1.3 ± 0.3</td>
<td>1.4 ± 0.4</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>Serum magnesium (mmol/l)</td>
<td>0.82 ± 0.1</td>
<td>0.8 ± 0.09</td>
<td>0.85 ± 0.11</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>54 ± 10</td>
<td>55 ± 9</td>
<td>82 ± 19</td>
</tr>
<tr>
<td>Serum ferritin (ng/ml)</td>
<td>108 ± 35</td>
<td>114 ± 40</td>
<td>133 ± 38</td>
</tr>
</tbody>
</table>

REFERENCES


