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CLINICAL INVESTIGATIONS

Effects of Oral Granisetron Treatment on Uremic Pruritus

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Abstract: The present study aimed to investigate the efficacy, safety, and tolerability of orally administered granisetron, a 5-HT_3 receptor antagonist, and its possible effect on serum histamine and serotonin levels in uremic pruritic patients who have not yet undergone dialysis.

Fourteen patients with newly diagnosed end-stage renal disease were asked to complete a questionnaire about pruritus, and histamine, serotonin, PTH and cortisol levels were measured on days 0, 7 and 14. Granisetron (1 mg) was administered twice daily for 2 weeks.

Plasma histamine levels were found to be up to 7 times higher in all patients and they did not change significantly during the study. Serum serotonin levels decreased significantly on days 7 and 14 of the study in women compared with men ($P < 0.05$). There was no significant change in the histamine X serotonin values except for the decrease in men on day 14 of the study ($P < 0.05$). Pruritus scores decreased at the end of the study compared with the beginning but this was not statistically significant. However, the decrease in pruritus scores in women on days 7 and 14 vas statistically significant ($P < 0.05$).

Pruritic uremic patients with end-stage renal disease and have not been undergone any of the renal replacement therapies, were found to have markedly elevated plasma histamine levels. Granisetron was found to be effective particularly in newly diagnosed female uremic patients.

Key Words: Renal failure, pruritus, granisetron, histamine, serotonin

Introduction

Ondansetron, a selective inhibitor of 5-hydroxytryptamine$_3$ (5-HT_3) receptors in the central and peripheral neural systems, has been used in some pruritic patients due to cholestasis of various etiologies and in uremic pruritic patients on peritoneal dialysis with satisfactory results (1-3). To the best of our knowledge the effects of 5HT3 receptor antagonists have not been investigated in patients who have not received any dialytic treatment. Our aim was to investigate the action mechanism of orally administered granisetron, a 5-HT_3 receptor antagonist, on pruritus among uremic patients who had not undergone any renal replacement therapy but were awaiting maturation of an arteriovenous fistula or a newly placed peritoneal dialysis catheter. Additionally, the efficacy, safety, and tolerability of orally administered granisetron were also evaluated and possible effects on histamine and serotonin levels were tested.

Materials and Methods

Fourteen predialytic uremic patients were included in the study. Out of the 14, diabetes mellitus was diagnosed in 3 (21.42%), chronic glomerulonephritis in 1 (7.14%), and obstructive uropathy in 1 (7.14%) and no underlying disease was found in the remaining 9 (64.28%).

The severity of pruritus was measured using a method proposed by Duo (4) and modified by Mettang et al. (5) and afterwards by Balaskas et al. (6). This method is based on criteria such as scratching, severity, frequency and distribution of pruritus, number of sleeping hours and frequency of waking up during the night because of itching. Pruritus was graded according to the total points for each patient as mild "1-16", moderate "17-32", and severe "33-48".

Biochemical parameters, plasma histamine, serum serotonin, PTH and cortisol levels were measured on days

0, 7 and 14. The patients were treated with granisetron (Kytril ® tablet) 1 mg twice daily for a mean duration of 2 weeks. All statistical values were analyzed by a nonparametric method. The differences between levels of histamine, serotonin, 'histamine X serotonin' products, PTH and cortisol were analyzed using the Wilcoxon test. The Spearman nonparametric correlation test was used for analyzing the correlations between all parameters. P less than 0.05 was considered significant.

Results

Fourteen patients (5 male and 9 female) with a mean age of 49.45 ± 15.1 years (range from 18 to 74 years) were evaluated. The severity of xerosis did not change in any patients during the study. There was no correlation between xerosis and age, sex, hematological and biochemical parameters, histamine, serotonin, 'histamine X serotonin' products and cortisol levels. There was a weak correlation between PTH levels and xerosis (P: 0.047). Mean pruritus scores were 26.00, 22.50 and 15.00 in the patients with mild xerosis; 30.20, 25.00 and 13.60 in the patients with moderate xerosis; and 28.42, 23.42 and 13.71 in the patients with severe xerosis on days 0, 7 and 14, respectively. There was a weak positive correlation between the presence and severity of pruritus and the severity of xerosis (P: 0.374, r: 0.258).

There was no statistically significant relationship between the sexes according to histamine, PTH, cortisol levels, or other hematological or biochemical parameters (Table 1).

Table 1. Biochemical parameters throughout the study.

		N	Mean ± SD	IQR
Serotonin day 0	Male	5	143.01 ± 27.71	41.00
	Female	9	164.82 ± 24.58	44.53
Serotonin day 7	Male	5	162.55 ± 35.13	68.64
	Female	9	143.56 ± 21.18 *	43.12
Serotonin day 14	Male	5	157.53 ± 26.51	42.01
	Female	9	159.72 ± 21.66 *	31.08
Histamine day 0	Male	5	4.10 ± 0.77	1.45
	Female	9	4.89 ± 1.39	1.57
Histamine day 7	Male	5	4.35 ± 0.96	1.46
	Female	9	4.98 ± 0.82	0.86
Histamine day 14	Male	5	4.40 ± 1.09	2.01
	Female	9	4.41 ± 0.75	1.02
Histamine X Serotonin day 0	Male	5	573.17 ± 62.77	119.51
	Female	9	795.51 ± 206.12	331.27
Histamine X Serotonin day 7	Male	5	695.33 ± 180.27	323.11
	Female	9	709.28 ± 128.01	136.96
Histamine X Serotonin day 14	Male	5	681.31 ± 151.79	299.51
	Female	9	708.19 ± 172.28	344.64
PTH day 0	Male	5	255.0 ± 371.9	458.5
	Female	9	428.1 ± 332.6	470.5
PTH day 7	Male	5	90.2 ± 54.9	99.5
	Female	9	453.4 ± 378.5	504.5
PTH day 14	Male	5	107.4 ± 46.6	92.5
	Female	9	383.6 ± 334.6	437.0
Cortisol day 0	Male	5	15.24 ± 9.64	12.94
	Female	9	12.78 ± 2.71	4.83
Cortisol day 7	Male	5	17.17 ± 9.65	13.06
	Female	9	13.57 ± 4.95	5.51
Cortisol day 14	Male	5	14.11 ± 1.69	3.10
	Female	9	11.06 ± 2.41	3.95

* $P < 0.05$

Plasma histamine levels were markedly increased in all patients, up to 7 times higher than the upper normal limit. Histamine levels did not change significantly during the study. Serum serotonin levels were not increased above normal values but presented fluctuations as in the normal healthy population. Serum serotonin levels were decreased significantly on days 7 and 14 in women compared to men ($P < 0.05$). We calculated the product 'histamine X serotonin' in all patients and there was no significant change in these values except for the increase in men on day 14, which was statistically significant ($P < 0.05$).

PTH and cortisol levels were measured in all patients. PTH levels showed fluctuations and increased up to 18 times higher than upper values. PTH levels were decreased on days 7 and 14 of the study in both sexes but this decrease was not statistically significant. There was no relationship between PTH levels and pruritus scores. There was also no relationship between cortisol levels and pruritus. An average negative correlation was found between mean cortisol levels and pruritus score on day 7 (P: 0.028, r: 0.028). Cortisol levels were decreased on days 7 and 14 but these decreases were not statistically significant.

Pruritus scores were decreased at the end of the study compared to the beginning but this decrease was not statistically significant. However, the decreases in pruritus scores in women on days 7 and 14 were statistically significant ($P < 0.05$) (Table 2).

Discussion

Pruritus and xerosis are the most common cutaneous manifestations in uremic patients (7-,8). The etiology of uremic pruritus remains unclear, and no therapy to date has been reliably effective (9,10). A longer time on dialysis may cause an increase in the prevalence and severity of pruritus (9). The results of the present study are independent of the dialysis, because all patients were newly diagnosed and had not chosen the type of renal replacement therapy.

Table 2. Pruritus scores during treatment.

	PRURITUS SCORE		
	Mean ± SD	Range	P
Before treatment	28.4 ± 5	16-36	-
1st week	23.6 ± 3.6	17-30	> 0.05
2nd week	14.1 ± 3.4	8-20	> 0.05

It is well known that xerosis may contribute to pruritus (6,11,12). It has been found that pruritic patients had lower water content in the stratum corneum layer of the skin than nonpruritics (12,13). In our study the water content of the stratum corneum was not measured but the severity of xerosis according to the physical examination was positively correlated with the pruritus scores.

It was reported that plasma histamine levels were increased in uremic patients (5,11,14,15). Some investigators reported a positive correlation between plasma histamine levels and pruritus (15,16), but others did not (11,17). In our study plasma histamine levels were noticeably increased but this was not correlated with the severity of pruritus.

Balaskas et al. reported that the measurement of serum serotonin levels revealed large fluctuations in pruritic patients as in healthy subjects (3). They also found that there was a difference between normal values and those of patients, but it was not statistically significant. In our study serum serotonin levels showed fluctuations but stayed within the normal ranges (3).

Balaskas et al. also reported that there was a greater difference between 2 groups of patients (CAPD and HD patients) when they calculated the 'histamine X serotonin' products (3). Because pruritus is possibly multifactorial we also tried to calculate the product of 2 possible mediators, histamine and serotonin, like the previous investigators. However, we could not find a relationship between these products and other parameters. We found fluctuating levels of serotonin but they were all within normal ranges. Fluctuations of serum serotonin levels may affect the severity of pruritus.

Secondary hyperparathyroidism and increased product of calcium and phosphorus (Ca X P) may play roles in the pathogenesis of pruritus in uremic patients as well (18). Chou et al. reported that pruritus in patients with secondary hyperparathyroidism can be reduced by parathyroidectomy and also they found the high levels of Ca X P was the only factor that seemed to affect the postoperative extent of pruritus (18). In our study there was a weak correlation between PTH levels and xerosis

but not with pruritus scores, confirming the previous study.

All uremic patients are under severe mental stress at the beginning of the disease (19). It has been shown that experimentally induced mental stress activates the psychoneuroendocrine systems and skin responses established as itch and flare (20). Basal and urinary cortisol levels were found to be increased in these patients. Hypercortisolemic state causes pruritus (21). We measured the basal cortisol levels depending on these data, but we did not find a correlation between basal cortisol levels and pruritus scores except for a positive correlation on day 7 of the study. Almost all of our patients had normal basal cortisol levels and cortisol levels were not related to the presence or severity of the pruritus.

Balaskas et al. administered ondansetron for the management of uremic pruritus in CAPD patients with satisfactory results (3). Based on the above findings we administered granisetron for the same purpose. Severity of pruritus decreased progressively, especially in women, but had not disappeared totally at the end of the second week of treatment. No side effects or complications were observed. Levels of histamine and serotonin were not decreased significantly at the end of our study, in contrast to the study by Balaskas et al.

We can conclude that granisetron acts on receptor level and its effects are not related to the blood levels of mediators, confirming the results reported by Weisshaar et al. (22). Weisshaar et al. demonstrated that tropisetron as a 5-HT_3 receptor antagonist did not affect histamine-induced itch but has a measurable effect on serotonin-induced itch. We think that the local release of histamine at the tissue level presumably causes pruritus, and plasma levels would be only a crude indicator of local tissue reactions.

In conclusion, pruritic uremic patients who had newly diagnosed end-stage renal disease and had not undergone any renal replacement therapy, were found to have markedly elevated plasma histamine levels and were more xerotic. None of the parameters that changed during the study can explain the improvement in pruritic symptoms. Serotonin levels did not elevate but showed fluctuations. However, we know that the number of patients was low in our study and so new studies have to be planned with larger groups.

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References

1. Schwörer H, Ramadori G. Improvement of cholestatic pruritus by ondansetron. Lancet 341: 1277, 1993.
2. Raderer M, Müller C, Scheithauer W. Ondansetron for pruritus due to cholestasis. N Eng J Med 30: 1540, 1994.
3. Balaskas EV, Bamihas GI, Karamouzis M et al. Histamine and serotonin in uremic pruritus: Effect of ondansetron in CAPD-pruritic patients. Nephron 78: 395-402, 1998.
4. Duo LJ. Electrical needle therapy of uremic pruritus. Nephron 47: 179-183, 1987.
5. Mettang T, Fritz P, Weber J et al. Uremic pruitus in patients on hemodialysis or continuous ambulatory peritoneal dialysis: the role of plasma histamine and skin mast cells. Clin Nephrol 34: 136-141, 1990.
6. Balaskas EV, Chu M, Uldall RP, Gupta A et al. Pruritus in continuous ambulatory peritoneal dialysis and hemodialysis patients. Perit Dial Int 3(suppl 2): 527-532, 1993.
7. Bencini PL, Montagnino G, Cittero A et al. Cutaneous abnormalities in uremic patients. Nephron 40: 316-21, 1985.
8. Masi CM, Cohen EP. Dialysis efficacy and itching in renal failure. Nephron 62: 257-61, 1992.
9. Balaskas EV, Oreopoulos DG. Uremic pruritus (Part I). Dial Transpl 21: 192-205, 1992.
10. Stahle-Backdahl M. Uremic pruritus: Clinical and experimental studies. Acta Derm Venereol (Stockh)145(suppl): 1-38, 1989.
11. Stockenhuber F, Kurz RW, Sertl K et al. Increased plasma histamine levels in uremic pruritus. Clin Sci 79: 477-482, 1990.
12. Raja RM. Uremic pruritus. Semin Dial 6: 350-352, 1993.
13. Stahle-Backdahl M. Uremic pruritus: Clinical and experimental studies. Acta Derm Venereol (Stockh) 145(suppl): 1-38, 1989.
14. Gill DS, Fonseca VA, Barradas MA et al. Plasma histamine in patients with chronic renal failure and nephrotic syndrome. J Clin Pathol 44: 243-245, 1991.

15. Dimcovic N, Djukanovic L, Radmilovic A et al. Uremic pruritus and skin mast cells. Nephron 61: 5-9, 1992.

16. Francos GC, Kauh YC, Gitllen SD et al. Elevated plasma histaminee in chronic uremia. Effects of ketotifen of pruritus. Int J Dermatol 30: 884-889, 1991.

17. Handwerker RD, Reeh PW, Steen KH. Effects of 5-HT on nociceptors; in Besson JM (ed): Serotonin and Pain. Amsterdam 1990, pp: 1-16.

18. Cho YL, Liu HN, Huang TP et al. Uremic pruritus: roles of parathyroid hormone and substance P. J Am Acad Derm 36: 538-43, 1997.

19. Fjellner B, Arnetz BB. Psychological predictors of pruritus during mental stress. Acta Derm Venereol 65: 504-8, 1985.

20. Rosenthal KL, Peterson ME, Quesenberry KE et al. Hyperadrenocorticism associated with adrenocortical tumor or nodular hyperplasia of the adrenal gland in ferrets: 50 cases. J Am Vet Med Assoc 203: 271-5, 1993.

21. Richardson BP. Serotonin and nociception. Ann NY Acad Sci 600: 511-520, 1990.

22. Weisshaar E, Ziethen B, Rohl FW et al. The antipruritic effect of a 5-HT_3 receptor antagonist (tropisetron) is dependent on mast cell depletion–an experimental study. Exp Dermatol 8: 254-60, 1999.