

Treatment of Uremic Pruritus With Gabapentin in Hemodialysis Patients

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Abstract

Background. Uremic pruritus is a common and annoying symptom in patients with chronic renal failure, especially those on hemodialysis, having a negative influence on their quality of life. Prevalence remains high despite the improvement of hemodialysis treatment. Gabapentin has proved to be effective in decreasing pain in peripheral diabetic neuropathy. Similarly, a decrease of uremic pruritus in patients with chronic renal failure has been observed. The study aims to evaluate the effectiveness and safety of low dose Gabapentin treatment in hemodialysis patients with uremic pruritus.

Methods. We enrolled in the study 8 patients (six men, two women) 70 ± 7.1 years old, on maintenance hemodialysis for 52.4 \pm 58.5 months. Each patient suffered from uremic pruritus for a quite long time and received classic treatment for it without significant response. All patients had been examined by a dermatologist to exclude other conditions of the skin. Written informed consent was acquired. Initial dose was 100 mg Gabapentin per os thrice weekly given at the end of every hemodialysis session under nurse supervision. Unless the improvement was noticeable, the dose was gradually titrated to 300 mg thrice weekly. Pruritus was measured using a Visual Analogue Scale and a questionnaire based on severity, distribution and frequency. Adverse actions possibly relating to the drug were recorded.

Results. According to the VAS, mean value of uremic pruritus was 3.94 ± 3.38 after treatment with Gabapentin, in comparison to 8.37 ± 0.92 before treatment (p: 0.0041). By using the questionnaire, corresponding values were 4.87 ± 3.64 and 10.12 ± 0.83 (p: 0.0018). One patient reported no improvement. Three patients reported slight somnolence, one patient headache and one dizziness. The symptoms were mild, and did not require interruption of treatment.

Conclusions. Careful titrating Gabapentin dosage in hemodialysis patients seems to have an alleviating effect on uremic pruritus an observation which is supportive to the neuropathic hypothesis of uremic pruritus pathogenesis.

Keywords: gabapentin; hemodialysis; neuropathic; uremic pruritus

Introduction

Pruritus is an unpleasant sensation that induces a desire to scratch. It is a common symptom of skin and systemic diseases

such as dermatitis, dermatoses, malignancy, endocrine disorders, myeloproliferative disease and psychiatric and neurologic diseases [1].

In patients with chronic kidney disease, pruritus presents a severe and distressing symptom which affects their sleep and quality of life [2]. The itching can be either generalized or localized. In the literature, the prevalence of pruritus in these patients, ranges between 22%-50% and despite the decline in the incidence over the years because of the efficacy of biocompatible hemodialysis used nowadays, remains one of the most challenging clinical problems for the nephrologist [2,3,4]. Treatment of uremic pruritus presents a difficult task, because its exact pathogenesis is not well perceived. Among the treatment modalities used, gabapentin -a relatively novel antiepileptic agent- is reported to be effective in patients with end stage renal disease (ESRD). The drug has an unknown mechanism of action and has been also proven to be effective against chronic pain syndromes of neuropathic origin, especially neuropathic pain of diabetes mellitus [5,6].

Gabapentin is eliminated through the kidney and it is removed by hemodialysis. It has a significant longer half life in patients on hemodialysis. The recommended dose is 200-300 mg after each hemodialysis session [7].

We undertook this study to evaluate the effectiveness and safety of low dose Gabapentin therapy in hemodialysis patients with uremic pruritus.

Patients and methods

We included 8 patients from our dialysis unit, six men and two women, 70 ± 7.1 years old [58-82]. All patients were on hemodialysis for 52.4 ± 58.5 months [3-178]. All were on a four hour thrice weekly outpatient hemodialysis schedule with biocompatible membranes and received adequate dialysis dose according to their KT/V value. Each one of them had suffered from uremic pruritus for quite long time and received classic treatments, without significant response. All patients had been examined by a dermatologist to exclude other skin conditions. None of the patients had concomitant skin, liver or metabolic diseases. Pre-dialysis blood chemistries of hemoglobin, serum calcium, phosphate and parathyroid hormone were observed. The patients were asked to evaluate the severity of their pruritus before each session on a Visual Analogue Scale (VAS). The scale consisted of a 10 cm horizontal line marked from 0 (denoting no itching) to 10 (denoting worst itching). Patients were also asked to answer a questionnaire based on severity,

distribution and frequency of pruritus by Duo, modified by Mettang and Hiroshige [8]. All patients reporting itching were given Gabapentin therapy in titrated doses. Starting dose was 100 mg per os given at the end of every hemodialysis session under nurse supervision. In case no significant improvement was reported, the dose was gradually titrated up to a maximum of 300 mg after each session. Furthermore, adverse reactions possibly relating to the drug were recorded.

Results are reported as mean±SD. Student's paire t-test was employed for statistical analysis of data before and after

Table 1. Demographics and Baseline characteristics

four weeks of gabapentin therapy. Statistical significance was assigned to p-value of < 0.05.

Written informed consent was requested and received from all patients.

Results

All patients completed the study which lasted four weeks. Their baseline characteristics are listed in Table 1.

no	sex	age (years)	time on HD (months)	previous treatment	skin lesions	membrane (m2)	KT/V	Ca (mg/dl)	P (mg/dl)	PTH (pg/ml)	Ferritin (ng/dl)	Hb (g/dl)
1	m	71	3	+	+	F8HPS(1.8)	1.6	8.7	5.3	248	131	13.0
2	m	70	5	+	-	KF201C(1.8)	1.5	8.5	4.6	30	349	10.1
3	f	70	178	+	+	F6HPS (1.3)	2.0	9.2	3.8	293	19	13.1
4	m	66	65	+	-	CL*E18 1.8)	1.7	9.1	3.3	183	235	11.9
5	f	82	85	+	+	F6HPS (1.3)	1.9	9.4	2.9	89	315	11.1
6	m	77	27	+	+	F10HPS(2.2)	1.5	9.2	4.5	183	42	12.0
7	m	58	43	+	+	F80S (1.8)	1.3	8.8	4.6	364	287	11.5
8	m	69	13	+	+	F10HPS (2.2)	1.5	8.5	2.9	50	89	12.2

According to the VAS, the mean pruritus score before the study was 8.37 ± 0.92 while at the end of the study it was 3.94 ± 3.38 (p: 0.0041). Using the Duo-Mettang question-

naire, corresponding values were 10.12 \pm 0.83 and 4.87 \pm 3.64 (p: 0.0018) (Fig. 1 and Fig. 2).



Fig.1: Changes in the Pruritus Scores (per patient)

Seven patients reported considerable improvement, three of them on 100 mg dose per session, two on 200 mg per session and two gradually receiving the maximum dose of 300mg per session. One patient, with atheroembolic disease as the cause of renal failure, reported no noticeable improvement even after three months (extended) treatment at the maximum dosage of gabapentin employed in this study (300 mg per hemodialysis session).



Fig. 2: Changes in the Pruritus Scores (Mean Value ±SD)

Three of the patients reported slight somnolence, one reported headache and one reported dizziness, complaints which could be related to Gabapentin treatment. In all cases, the symptoms were mild and did not require interruption of treatment.

Discussion

In patients with chronic renal failure, uremic pruritus continues to be a frequent and particularly annoying symptom, especially in those undergoing dialysis. It affects sleep, interferes with work and potentially compromises quality of life [3,4]. It is paroxysmal and often remits spontaneously.

Uremic pruritus has a complex and unclear physiology. The pathogenetic mechanisms remain obscure and probably for these reason most treatments are ineffective. In the literature, several factors are implicated in the pathogenesis of itching. The role of secondary hyperparathyroidism remains prominent as well as the derangements of calcium and phosphorus metabolism [9]. Although parathormone (PTH) itself is not pruritogenic when injected into the skin, elevated [Ca] x [P] product is correlated with itching. It is also suggested, that the above described factors, elevated histamine levels, somatic neuropathy and opioid receptors play a possible role in the pathogenesis of uremic pruritus. Several other factors are implicated in the pathogenesis such as xerosis (dry skin) high serum levels of magnesium, aluminium, substance P, hypervitaminosis A, peripheral neuropathy and anemia [1,10].

The neurophysiology of pain and pruritus is similar. Both are conveyed by a subset of specialized C-fibers in the dorsal horns of two separate systems and transmitted to the thalamus and the somatosensory cortex via the lateral spinothalamic tract. It is known that painful scratching reduces itching and this can be explained because of the interaction of the pain and itching pathways [11]. It is suggested that uremic pruritus could be due to a diminished threshold of perception, regardless of the specific causative factor. This can be the result of the peripheral nerve fiber damage due to uremic neuropathy associated with a central sensitization to itch, which is chronically sustained by the uremic toxins [12].

Many treatment options have been tested. Among others, antihistamines are currently the most widely used drugs. Opioid antagonists, the serotonin receptor blocker ondansetron, antipruritic lotions, ultraviolet therapy, tacrolimus, lidocaine and capsaicin have also been used although with clinically contradictory results [1,10].

The correlation between chronic pain and pruritus suggests that treatment for uremic pruritus, beside the antipruritic agents such as antihistamines, could also include pain modulators. In the context of this suggestion, Gabapentin has been used in the treatment of uremic pruritus [13,14].

Gabapentin is an antiepileptic drug which experimentally blocks the tonic nociception phase and exerts a potent inhibitory effect in different models of neuropathic pain. It seems to have a central rather a peripheral effect [15]. In the literature, gabapentin has been reported to be effective in relieving the symptoms of brachioradial pruritus [16,17] another form of neuropathic itch. Also, there are some studies which show that gabapentin can successfully control the uremic pruritus in hemodialysis patients [13,14]. Patients included in our study had long lasting, treatmentresistant pruritus and no evidence of dermatological disease. In order to exclude factors possibly aggravating uremic pruritus, such as anemia and inadequate dialysis, only patients who were considered to be well dialyzed, with a hemoglobin level >10g/dl were included in our study. Our patients did have neither hyperphosphatemia nor hyperparathyroidism as the pathogenetic role of these factors in uremic pruritus is controversial.

Our results point to the effectiveness of gabapentin treatment in relieving pruritus in hemodialysis patients supporting the hypothesis for the neuropathic origin of uremic pruritus. Gabapentin was effective in all but one patient who did not respond to the treatment. Therefore it may be assumed that one or both of neuropathic and neurogenic mechanisms may be responsible for the renal itch. It was shown that gabapentin is well tolerated with only a few side effects (slight somnolence, headache and dizziness) which did not require the interruption of therapy. It is possible that initiating therapy with a lower dose and titrating it slowly up or downwards as well as the nurse supervision makes gabapentin treatment safe and effective.

Conclusions

In conclusion, our results support the suggestion that gabapentin is a therapeutic option for itching in hemodialysed patients which can be safe, well tolerated and effective.

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Conflict of interest statement. None declared.

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