

Original Article

Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial

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Abstract

Background. Uraemic pruritus is a common and distressing symptom in patients on haemodialysis for chronic renal failure. Gabapentin is an anticonvulsant that alleviates neuropathic pain. We conducted a double-blind, placebo-controlled, crossover study to assess its effectiveness against renal itch.

Methods. We enrolled in the trial 25 adult patients on haemodialysis who were asked to daily record the severity of their pruritus on a visual analogue scale. The patients were randomly assigned to receive gabapentin for 4 weeks followed by placebo for 4 weeks or the reverse sequence. Gabapentin or placebo were administered thrice weekly, at the end of haemodialysis sessions.

Results. The mean pruritus score of the cohort before the study was 8.4 ± 0.94 . After placebo intake, it decreased to 7.6 ± 2.6 ($P = 0.098$). The score of four patients decreased by $>50\%$ following placebo. After gabapentin administration, the mean score decreased significantly, to 1.2 ± 1.8 ($P = 0.0001$), although one patient's symptoms did not improve significantly. No patient dropped out of the study due to adverse effects from gabapentin.

Conclusions. Our study shows that gabapentin is safe and effective for treating uraemic pruritus in haemodialysis patients. Our results also support the neuropathic hypothesis of uraemic pruritus.

Keywords: gabapentin; haemodialysis; uraemic pruritus

Introduction

Uraemic pruritus is commonly experienced by patients suffering from advanced chronic renal failure who

already are on renal replacement treatment (haemodialysis or continuous ambulatory peritoneal dialysis). Because of the use of biocompatible haemodialysis membranes and the improvement in haemodialysis efficacy, the incidence of uraemic pruritus has declined over the years, from an estimated 85% in the 1970s and 50–60% in the 1980s to a current estimated incidence of 22% [1]. The mechanism of uraemic pruritus is unknown and most treatments are ineffective. Several hypotheses have been proposed to explain the pathogenesis of uraemic pruritus. Its suggested causes include xerosis [2], involvement of the peripheral nervous system [3,4], opioid system involvement [5], mast cells and autacoids (histamine and serotonin), altered divalent ion metabolism, hyperparathyroidism [6] and derangements of the immune system [7]. Currently, there are two major concepts, however, for the pathophysiology of uraemic pruritus, the opioid and the cytokine hypotheses.

Gabapentin is a potent anticonvulsant drug with an unknown mechanism of action. Initially approved only for use in controlling seizures, it soon showed promise in the treatment of chronic pain syndromes, especially neuropathic pain [8], and it has been clearly demonstrated to be effective for the treatment of neuropathic pain in diabetic neuropathy.

Gabapentin is eliminated primarily through the kidney. Moreover, it is removed by haemodialysis. It has a significantly longer half-life in patients on haemodialysis than in those with normal renal function and, thus, these patients need lower doses at less frequent intervals than patients with normal renal function. The recommended dose for haemodialysis patients is 200–300 mg after each haemodialysis session [8].

We use gabapentin for the relief of diabetic neuropathic pain in patients on haemodialysis in our centre. In addition to neuropathic pain, several of our patients have complained of pruritus and after gabapentin treatment, their pruritus has completely improved. Accordingly, we undertook a double-blind,

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placebo-controlled, crossover trial to assess the effectiveness of gabapentin against renal itch.

Subjects and methods

From the haemodialysis unit in Firat University Hospital, we enrolled in the study 25 adult patients (14 men and 11 women; age: ≥ 18 years) all of whom were on haemodialysis and eight of whom were diabetic. Haemodialysis was performed for 4–5 h thrice weekly via a polysulphone dialyser [1.3–1.6 m² surface area (Fresenius Medical Care, Bad Homburg, Germany)] using bicarbonate dialysis fluid containing 136 mmol/l Na, 1.5 mmol/l Ca, 0.5 mmol/l Mg, 110 mmol/l Cl, 2 mmol/l acetate and 33 mmol/l bicarbonate. Blood flow and dialysate flow were 250–350 and 500 ml/min, respectively. Ultrafiltration was controlled volumetrically in all haemodialysis machines used in this study. All patients had histories of pruritus of >8 weeks duration. Their pruritus was not relieved by antihistamines, nicergoline or moisturizers. None of the patients had concomitant dermatological, liver or metabolic diseases associated with pruritus. Any medication with presumed antipruritic effects was discontinued 1 week before the study. The patients were asked to record the severity of their pruritus on a visual analogue scale once a day. The scale consisted of a 10 cm horizontal line marked from 0 (denoting no itch) to 10 (denoting worst possible imaginable itch). On a random and blinded basis, patients were assigned to receive 4 weeks of gabapentin therapy followed by 4 weeks of placebo or to the reverse sequence (4 weeks of placebo followed by gabapentin for 4 weeks). There was a 1 week washout period between the sequential treatment phases. The daily pruritus scores of patients were collected for each period of the study – the 1 week preceding the trial, the active treatment phase, the placebo phase and the intervening washout period. The median of the scores for each period was accepted as the score of that period. Gabapentin 300 mg (Neurontin; Parke-Davis, Goedecke GmbH, Freiburg, Germany) or placebo was administered orally thrice weekly at the end of haemodialysis sessions. A reduction in scores of $\geq 50\%$ was considered as the desired improvement in symptoms during treatment. Pre-dialysis blood samples were drawn for haematocrit, serum calcium, phosphate, albumin and parathyroid hormone levels. Dialysis efficacy was calculated using the urea kinetics model and expressed as Kt/V_{urea} . The differences in mean values were tested by a one-way analysis of variance. The significance of the differences between the groups was calculated by the paired-samples *t*-test. Statistical significance was assigned to *P*-values of <0.05 .

The Ethics Committee of Firat University Hospital approved the study design. Informed consent was obtained from each patient.

Results

All 25 patients completed the study. Their demographic characteristics are listed in Table 1. The mean pruritus score before the study was 8.4 ± 0.94 (range: 7–10). After placebo administration, that score decreased to 7.6 ± 2.6 (range: 2–10; $P=0.098$). The scores of four patients decreased by $>50\%$ with

placebo. These four patients with good response to placebo were not different from other patients with respect to their plasma levels of phosphate, parathyroid hormone, albumin and dialysis efficiency. After the 1 week washout period, the mean pruritus score returned to the baseline levels (7.9 ± 1.1). After gabapentin administration, the mean score decreased significantly to 1.2 ± 1.8 (range: 0–8; $P=0.0001$; Figure 1). Only one patient's symptoms did not improve significantly with gabapentin. Somnolence, dizziness and fatigue were the most common side effects of gabapentin noticed during the trial. These adverse effects were mild to moderate and commonly occurred after the first dose of the drug. They usually subsided within 7 days from the initiation of the treatment. None of the patients was forced to drop out of the study due to adverse effects from gabapentin.

Table 1. Patient characteristics

Parameter	Means \pm SD	Minimum	Maximum
Age (years)	55 \pm 11	32	77
Dialysis duration (months)	42 \pm 33	3	111
Systolic pressure (mmHg)	112 \pm 17	70	140
Diastolic pressure (mmHg)	68 \pm 13	40	90
Cardiothoracic ratio (%)	46 \pm 4	38	55
Haematocrit (%)	31.4 \pm 4.4	22.7	42
Serum albumin (g/dl)	3.9 \pm 0.6	2.8	4.6
Calcium (mg/dl)	8.6 \pm 0.9	6.9	10.8
Phosphate (mg/dl)	4.5 \pm 1.2	2.2	6.5
Calcium \times phosphate (mg/dl)	39 \pm 12	17	58
Parathyroid hormone (pg/ml)	186 \pm 130	10	472
Kt/V_{urea}	1.37 \pm 0.35	0.5	1.93
nPCR (g/kg/day)	1.36 \pm 0.41	0.52	2.16

nPCR, normalized protein catabolic rate.

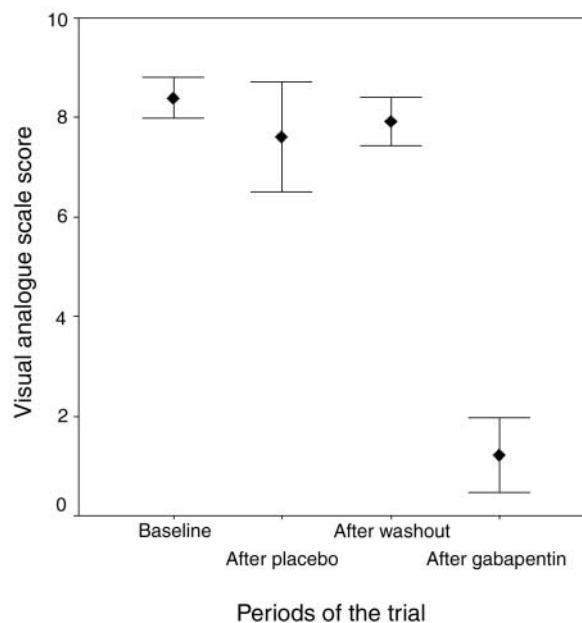


Fig. 1. Changes in the pruritus scores before and after interventions.

Discussion

The neuropathic hypothesis is the basis of the therapeutic approach we chose for our patients. Neuropathy frequently occurs in uraemic patients, with $\geq 65\%$ of patients with renal failure exhibiting a dysfunction of the peripheral nervous system [9]. It has been suggested that the activity of the nervous system plays an important role in the mechanism of uraemic pruritus [3]. Abnormal nerve conductions in both motor and sensory circuits are common concomitants of the early manifestations of uraemia, such as paraesthesias, burning feet and restless leg syndrome [3]. Pruritus may arise from a diminished threshold of perception. This augmented sensitivity to pruritic stimuli may result from nerve fibre damage. It has been demonstrated that uraemic patients on haemodialysis develop abnormal innervation. In them, but not in controls, nerve terminals and fibres have been found sprouting throughout the layers of the epidermis [4]. Moreover, the efficacy of topical capsaicin cream used to treat uraemic pruritus supports the relevance of the neurogenic hypothesis [10]. Substance P may be acting as a neurotransmitter in uraemic pruritus. It is known that capsaicin can deplete substance P from the peripheral neurons and thereby can alleviate itching [11].

Two previous case reports [12,13] showed gabapentin to successfully relieve the symptoms of brachioradial pruritus, another form of neuropathic itch. These case reports, which confirm our results, suggest that gabapentin may have a role in controlling the symptoms of neuropathic pruritus.

Because its pathophysiology is poorly understood, the treatment of uraemic pruritus remains mainly empirical. The therapies in use are generally of insufficient efficacy, failing to provide adequate and long-lasting relief. We report a double-blind, placebo-controlled, crossover trial to assess the effectiveness of gabapentin in the renal itch for the first time. Our results clearly show the impressive effectiveness of gabapentin treatment to relieve pruritus. Gabapentin is an anticonvulsant structurally related to the neurotransmitter γ -aminobutyric acid (GABA). Although its mechanism of action is not clear, gabapentin appears to have an effect on voltage-dependent calcium-ion channels. By inhibiting neuronal calcium influx, it may interrupt the series of events that perhaps lead to the pruritic sensation in uraemia [8].

It is most likely that uraemic pruritus is a mixture of both neuropathic and neurogenic itch. Neuropathic itch can originate from damage of the nervous system located at any point along the afferent pathway. Post-herpetic neuralgia and HIV infection are among conditions that underlie this category of itch. An itch originating centrally, but without neural damage, is termed neurogenic itch. Cholestasis and the administration of exogenous opioids underlie this

type of itch. In neurogenic itch, there is an increase in the opioidergic tone caused by the accumulation of endogenous opioids [11,14]. In our study, gabapentin treatment impressively relieved pruritus in all but one patient, who did not respond to the treatment. Therefore, it may be assumed that renal itches are of neuropathic origin in the majority of cases and neurogenic in the minority, which suggests that one or both of neuropathic and neurogenic mechanisms may underlie the renal itch.

Although our results are intriguing, one great disadvantage that limits this study is that pruritus was scored only once a day and the scores were only subjective indications of the severity of itching.

In summary, our study shows that gabapentin is a safe and effective therapy for uraemic pruritus in haemodialysis patients. Our results may also be interpreted as supporting the neuropathic hypothesis of uraemic pruritus.

Conflict of interest statement. None declared.

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