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

**Subjects and methods**

From the haemodialysis unit in Fırat 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, Goeddecke GmbH, Freiburg, Germany) or placebo was administered orally thrice weekly at the end of haemodialysis sessions. A reduction in scores of ≥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 Fırat 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>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tbody>
<tr>
<td>Parameter</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Dialysis duration (months)</td>
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<tr>
<td>Systolic pressure (mmHg)</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
</tr>
<tr>
<td>Cardiothoracic ratio (%)</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
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<tr>
<td>Serum albumin (g/dl)</td>
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<tr>
<td>Calcium (mg/dl)</td>
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<td>Phosphate (mg/dl)</td>
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<tr>
<td>Calcium x phosphate (mg/dl)</td>
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<tr>
<td>Parathyroid hormone (pg/ml)</td>
</tr>
<tr>
<td>Kt/V urea</td>
</tr>
<tr>
<td>nPCR (g/kg/day)</td>
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nPCR, normalized protein catabolic rate.

![Fig. 1. Changes in the pruritus scores before and after interventions.](https://academic.oup.com/ndt/article-abstract/19/12/3137/1807510/Gabapentin-therapy-for-pruritus-in-haemodialysis)
Discussion

The neuropathic hypothesis is the basis of the therapeu-
tic approach we chose for our patients. Neuropathy
frequently occurs in uraemic patients, with ≥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 parasthesias,
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 abnor-
mal 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 neuro-
genic hypothesis [10]. Substance P may be acting as
a neurotransmitter in uraemic pruritus. It is known
that capsaicin can deplete substance P from the periph-
eral 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 sym-
toms 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 neuro-
transmitter 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 path-
way. 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
derogenous 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
advantage 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 inter-
preted as supporting the neuropathic hypothesis of
uraemic pruritus.

Conflict of interest statement. None declared.

References


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