

Uraemic Pruritus: Relief of Itching by Gabapentin and Pregabalin

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Key Words

Uraemia · Pruritus · Itch · Gabapentin · Pregabalin · Dialysis · Chronic kidney disease

Abstract

Background: Pruritus (skin irritation or itching) is common in patients with chronic kidney disease (CKD) stages 4 and 5. It is associated with disrupted sleep, reduced quality of life, depression and increased mortality. A video of a patient describing the symptoms is at vimeo.com/49458473. **Methods:** We used gabapentin or pregabalin in 71 consecutive patients, 82% male. 25 had CKD stage 4 or 5, median eGFR = 17, range 9–30; 40 were on haemodialysis; 6 on peritoneal dialysis. Median itch severity score out of 10 = 8, range 6–10; median duration of itching = 6 months, range 0.5–240. Serum calcium ≤ 2.60 mmol/l (≤ 10.4 mg/dl) in 87% patients, phosphate ≤ 1.8 mmol/l (≤ 5.6 mg/dl) in 75%. 63% had used antihistamines and not gained relief. Starting dose of gabapentin 100 mg after dialysis or daily. Patients intolerant of gabapentin were offered pregabalin, starting dose 25 mg after dialysis or daily. **Results:** Gabapentin relieved itching in 47 patients (66%). A video of a patient describing the effect is at vimeo.com/49455976. 26 patients (37%) suffered side effects from gabapentin. Of 21 patients who stopped gabapentin due to side effects, 16 started pregabalin. Pregabalin relieved itching in 13 patients (81%). In total, gabapentin or pregabalin relieved itching in 60 patients (85%), median follow-up 2 months (range 1–8 months). Median

itch severity out of 10 reduced from 8 to 1. **Conclusions:** Gabapentin or pregabalin relieved itching in 85% of 71 consecutively treated CKD patients. Patients should be advised about side effects and the drug initiated at a low dose. Patients intolerant of gabapentin may tolerate pregabalin.

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Introduction

Pruritus (skin irritation or itching) is common in patients with chronic kidney disease (CKD) stages 4 and 5. For many patients, the symptoms are much more than intermittent irritations relieved by a satisfying scratch. 32% of haemodialysis (HD) patients are moderately or very much bothered by itchiness and 10% extremely bothered [1]. HD patients with moderate or severe itch are significantly more likely to feel drained or depressed and have a 17% higher mortality risk [1], statistically associated with the quality of sleep [1]. A patient's description of these symptoms and their impact is at vimeo.com/49458473.

HD patients with itching and pain due to diabetic neuropathy were found to be relieved of both symptoms by gabapentin [2, 3]. This suggests that GABA-dependent C-terminal afferent nerve fibres mediate uraemic pruritus. Gabapentin is an analogue of the inhibitory neurotransmitter gaba-aminobutyric acid, GABA. Pregabalin (Lyrica®) is a similar, more potent drug. They are

mainly used in the treatment of epilepsy and neuropathic pain. They are eliminated by renal excretion as unchanged drug. Common side effects include dizziness and drowsiness.

A randomised double-blind placebo controlled cross-over trial of gabapentin in 25 HD patients aged 32–77 years showed a dramatic reduction in the severity of itch [2]. Similar results in HD patients have been reported in two subsequent trials [4, 5] and a small case series [3]. There have been two reports of relief of renal itch with pregabalin [6, 7].

We report our experience of using gabapentin and pregabalin to treat pruritus in a cohort of patients with CKD stages 4 and 5 from a wide age range, including those receiving peritoneal dialysis and HD.

Methods

The Heart of England NHS Foundation Trust provides nephrology services to the population of approximately 800,000 in East Birmingham and the surrounding area. This is a socioeconomically and ethnically diverse community. In December 2012, the service was treating 407 patients on HD and 47 on peritoneal dialysis. 450 patients were receiving care for CKD stages 4 and 5 prior to renal replacement therapy. Subjects with itching were identified during routine consultations.

Itch severity was assessed before treatment using a scale ranging from 0 to 10 where 10 was the most severe itch imaginable. Patients whose itching was sufficiently troublesome, persistent and unrelieved by simple emollients or antihistamines were offered gabapentin treatment. Patients were advised that gabapentin was not licenced in the UK for this indication and were warned of possible side effects, particularly drowsiness. Patient gave verbal consent to be included in this report.

Gabapentin was started at 100 mg once daily for CKD and peritoneal dialysis (PD) patients and at 100 mg after dialysis for HD patients. Patients adjusted the dose regimen according to their symptoms in collaboration with their physician. Verbatim descriptions of quality of life before and during gabapentin treatment were noted. One patient gave written consent for an interview to be video recorded and made available via the Internet.

Patients who were unable to continue gabapentin due to side effects were offered pregabalin, starting at 25 mg once daily for CKD and PD patients and 25 mg after dialysis for HD patients.

Patients were prescribed gabapentin or pregabalin as an open label drug. There was no placebo or control group.

Results

Results on 71 consecutive patients with severe itching (score $\geq 6/10$) started on gabapentin since February 2012 are presented. Itching had been present for a median of 6

months. Patients were severely affected by itching, 87% having sleep disturbance and 66% making themselves bleed from scratching. Details of their demographics, symptoms, previous treatment, dosage and response to gabapentin are given in table 1.

63% had tried antihistamines with limited or no effect. One had gained no benefit from a course of UV therapy. The majority had serum calcium (corrected for serum albumin) and phosphate levels below the upper limit of recommended ranges (87% calcium <2.60 mmol/l, <10.4 mg/dl; 75% phosphate <1.8 mmol/l, <5.6 mg/dl).

47 (66%) gained relief of itch from gabapentin. Median itch severity was 1 (range 0–6) after median treatment duration of 2 months (range 1–8).

The following are verbatim reports from patients whose itching was relieved:

‘You prescribed gabapentin and she took one 100 mg capsule on Friday evening after dialysis. She felt drowsy after half an hour and then had the most remarkable 2 days of relief from the itching I have seen for many years. On Monday some symptoms re-appeared... she [took] another capsule [on] Monday evening after dialysis. The relief was the same, with another peaceful and undisturbed night’s sleep (for both of us!). We cannot thank you enough for prescribing this medicine. It has given E peace of mind, the strain has dropped from her face and she is much more positive about her condition and treatment.’ Patient E.

They are ‘magic pills’. I’m a ‘new man’. ‘Let other people who suffer from itching try this.’ Patient D.

‘After 2 h the itching went off like a light switch.’ ‘I am a different man.’ Patient J.

‘I’m still itching in the mornings when I get up but once I have my tablet of gabapentin I stop itching for the rest of the day, until late evening and perhaps once during the night. But Wow I’ve been catching up on my sleep! Therefore, I have had so much more energy during the day and feel my depression lifting!’ Patient V.

‘I have found I need to take a tablet during the weekend – later Saturday or Sunday morning as the itching starts to return so a dosage of 100 mg 4 times weekly seems appropriate for me. I do notice that towards the end of the dialysis session I am starting to itch so glad to take the tablet once the session has ended.’ Patient N.

A video of one patient’s experience of using gabapentin can be seen at vimeo.com/49455976.

Twenty-six patients (37%) suffered side effects from gabapentin: over-sedation (12), dizziness (6), tight chest/breathlessness (3), shaking limbs (2), vomiting (2), blotchy rash (2), nightmares (1), cramps (1), hair loss (1), low BP (1), incontinence (1); some patients had multiple side effects. 24 (34%) stopped gabapentin: 3 due to lack of effect on itching, 21 due to side effects.

Of the 21 who stopped gabapentin due to side effects, 16 were treated with pregabalin (table 2). 13 (81%) gained

Table 1. Details of patients treated with gabapentin

Gabapentin	CKD	HD	PD
Number of patients	25	40	6
M:F	15:10	31:9	6:0
Age, median (range), years	74 (33–90)	64 (35–88)	65 (42–80)
eGFR, median (range), ml/min/1.73 m ²	17 (9–30)	N/A	N/A
Duration of RRT, median (range), months	N/A	22 (1–324)	15 (5–88)
Serum Ca, albumin-corrected, median (range), mg/dl, mmol/l	9.44 (8.60–10.48) 2.36 (2.15–2.62)	9.78 (7.16–11.52) 2.45 (1.79–2.88)	10.32 (9.36–10.40) 2.59 (2.34–2.68)
Serum phosphate, median (range), mg/dl, mmol/l	4.37 (3.00–6.04) 1.41 (0.97–1.95)	4.75 (2.2–8.85) 1.54 (0.71–2.86)	4.58 (2.91–5.73) 1.49 (0.94–1.86)
PTH, median (range), pg/ml	213 (27–509)	230 (3–1166)	472 (14–713)
Duration of itching, median (range), months	7 (2–72)	6 (0.5–240)	2 (1–30)
Severity of itch, median (max = 10)	8 (6–10)	9 (6–10)	8 (7–10)
Sleep disturbance, yes (%)	21 (84%)	35 (88%)	6 (100%)
Bleeding from scratching, yes (%)	15 (60%)	26 (65%)	6 (100%)
Previous antihistamines, yes (%)	19 (76%)	23 (58%)	3 (50%)
Itch response: (1) side effects, gabapentin stopped (2) no reduction of itch, gabapentin stopped (3) significant reduction of itch: n	10:2:13	8:1:31	3:0:3
Final dose of gabapentin	13@100 mg o.d. 4@100 mg b.d. 5@200 mg o.d. 2@300 mg o.d. (1 missing)	13@100 mg after dialysis 2@300 mg after dialysis 1@400 mg after dialysis 11@100 mg daily 6@200 mg daily 5@300 mg daily 1@400 mg daily 1@900 mg daily	3@100 mg o.d. 1@200 mg o.d. 1@300 mg o.d. 1@200 mg 2 weekly
Length of follow-up, median (range), months,	1 (1–4)	2.5 (1–8)	1 (1–5)

Table 2. Details of patients treated with pregabalin

Pregabalin	CKD	HD	PD
Number of patients	6	6	3
Itch response: (1) side effects, pregabalin stopped (2) no reduction of itch, pregabalin stopped (3) significant reduction of itch: n	1:1:4	0:0:6	0:0:3
Final dose of pregabalin	2@25 mg o.d. 1@50 mg o.d. 2@75 mg o.d. 1@75 mg b.d.	1@25 mg after dialysis 2@25 mg o.d. 3@50 mg o.d.	1@25 mg o.d. 1@25 mg b.d. 1@50 mg o.d.
Length of follow-up, median (range), months	1 (1–4)	2 (1–4)	2 (1–3)

relief of itch from pregabalin. Median itch severity was 2 (range 0–5) after median treatment duration of 2.5 months (range 1–4). 3 stopped pregabalin: 1 due to lack of effect on itching, 2 due to side effects (oversedation in both).

Combining both treatments, 60 of the 71 patients (85%) gained significant relief of their itch and continued taking the tablets. For most, the effect was noticeable after taking the first one or two doses or after an increase in dose.

No significant attenuation of the effect was reported. Two patients' itching returned when gabapentin was stopped because of supply problems; restarting it relieved the itching again. Four patients stopped taking gabapentin or pregabalin and remained free of itch.

Relief of itch was achieved in some patients with skin conditions associated with itching. One had pruritus nodularis and 2 had chronic idiopathic urticaria. One patient with chronic eczema on the head and neck gained complete relief of itching on the limbs and partial relief in eczematous regions.

Six patients had improvement in pain conditions. Peripheral neuropathic pain was relieved in 3 patients, severe headaches and neck pain improved in 1 and joint pains and phantom limb pain improved in 1 each.

Discussion

This is the largest cohort study to date on the use of gabapentin and pregabalin to treat severe itching in a population of patients with CKD stage 4 and 5, including those on HD and PD.

Healthcare professionals may underestimate the impact of itching on the lives of some patients with CKD. The unremitting symptoms stop the patient from relaxing or sleeping. Patients and their partners become drained and depressed. Two patients' lives were so affected by itch that they considered stopping HD: 'It controls my life; it drives me mad.' A vivid description by one affected patient is at vimeo.com/49458473.

Itching is commonly attributed to high levels of serum calcium or phosphate. This can lead to a focus on intensifying diet and phosphate binders to treat itch. Our experience confirms data from the DOPPS showing that the mean values in patients with moderate or severe itch were only very slightly increased, 0.25 and 0.04 mg/dl (0.08 and 0.01 mmol/l), respectively [1]. The association with high serum calcium and phosphate may not be causal.

The marked male predominance of patients with itch in this series (82%) is consistent with the DOPPS study of HD patients [1]. It is not known why males are more affected.

The available treatments for uraemic pruritus have been recently reviewed in detail [8]. Antihistamines are commonly used based upon their effect on urticarial itch. However, there have been no well-conducted randomised controlled trials of antihistamines for renal itch. Anecdotal experience indicates that they are rarely if ever

effective apart from their mild sedative effect. The patients' description of renal itch differs from histamine-mediated urticaria; renal itch is felt below the surface of the skin.

Gabapentin also has been shown to relieve itching in controlled trials involving patients with itch due to burns and IL-2 treatment [9, 10] but not cholestasis [11].

In the current prospective study of 71 consecutively treated patients, 85% of patients treated with gabapentin or pregabalin gained substantial or complete relief from their itching whilst taking the drug. As this was not a randomised placebo-controlled study, it cannot be proved that the drug was responsible for the effects reported. However, the degree of reduction in itch was consistent with previous placebo-controlled trials. Furthermore, patients reported a clear dose-response relationship between gabapentin/pregabalin and itch severity and titrated their treatment according to the response. Four patients stopped the drug without the itch returning, consistent with marked fluctuation in the severity of itching week-to-week in some patients described in a detailed longitudinal study [12].

In the current study, 30% of patients experienced significant side effects with gabapentin and 12% with pregabalin, most commonly oversedation. It was not possible to predict which patients would suffer side effects. In the previous randomised trial of gabapentin [3] side effects were mild to moderate and usually subsided within 7 days. None of the patients in that trial dropped out. Patients in our study may have been more prone to adverse effects due to greater age and comorbidity.

Gabapentin and pregabalin should be started cautiously with close feedback between physician and patient. We routinely started with 100 mg gabapentin after dialysis for HD patients or once daily at night in CKD and PD patients. Others have also found this to be a more appropriate starting dose than the 300 mg used in the original RCT [4, 5]. The starting dose of pregabalin was 25 mg. The effects of the drug were noticed after one or a few doses, allowing rapid dose adjustment. Patients should be warned about possible sedation and dizziness. Patients with mobility difficulties or at risk of falls should be supervised for at least 12–24 h after the first dose.

Some patients had pain syndromes as well as itch and gained relief of both symptoms. Relief of itch by gabapentin in patients with peripheral neuropathic pain was the clue that led Gunal et al. [2] to carry out the initial randomised controlled trial. A recent study has shown similar relief of itch and pain with gabapentin and pregabalin in HD patients [7].

Many patients reported improved sleep quality and mood, beyond that due to the relief of itching. This is consistent with the demonstration of improved sleep quality and reduction in depression due to gabapentin and pregabalin in HD patients with neuropathic pain [13].

Conclusions

Clinicians should enquire about skin irritation and itching during consultations. Patients may be reluctant to admit to these symptoms due to embarrassment or a belief that they are caused by non-adherence to diet or phosphate binder therapy.

In patients with CKD and itching that persists despite attempts to correct calcium and phosphate balance and treatment with emollient creams, gabapentin is the drug

of first choice based upon the results of a controlled trial [2]. Pregabalin may be effective in patients unable to tolerate gabapentin.

These treatments should be promoted widely amongst the kidney community so that affected patients can be relieved of this distressing and debilitating symptom.

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