# Prurido urêmico em pacientes em hemodiálise: tratamento com desloratidina versus gabapentina

## Uremic pruritus in hemodialysis patients: treatment with desloratidine versus gabapentin

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Os autores declaram a inexistencia de conflitos de interesse.

## RESUMO

**Introdução:** Prurido urêmico é comum entre pacientes em diálise. Tratamentos eficazes não estão disponíveis até o momento. Provas recentes com anti-histamínicos e gabapentina indicam vários efeitos. **Objetivo:** Comparar a eficiência e os efeitos colaterais da gabapentina e da desloratadina em pacientes com prurido na diálise. **Métodos:** Estudo prospectivo, aberto e comparativo com 22 pacientes em hemodiálise crônica com prurido constante durante um período de pelo menos 60 dias. Após uma semana, submetemos os pacientes a três semanas de gabapentina 300 mg, três vezes por semana, ou desloratadina 5 mg três vezes por semana. Após um período de eliminação de uma semana, os pacientes trocaram de regime por mais três semanas. O objetivo primário do estudo foi a mudança na escala visual analógica (EVA) de prurido. **Resultados:** Dezenove indivíduos completaram os dois tratamentos e foram submetidos à análise. Os escores da EVA caíram com ambos os tratamentos (5,95 para 4,6 com gabapentina, p = 0,07; 5,89 para 3,4 com desloratadina, p = 0,004), mas somente a desloratadina teve significância estatística. Nenhuma diferença foi observada ao comparar o escore final do prurido com gabapentina e desloratadina (4,6 *versus* 3,4, p = 0,16). Excesso de sedação foi comum com gabapentina. A desloratadina teve alto nível de tolerância. **Conclusão:** A desloratadina dá alívio significante do prurido urêmico quando comparada a nenhum tratamento. A gabapentina tem eficiência marginal. A desloratadina tem maior nível de tolerância em relação à gabapentina.

**Palavras-chave:** Prurido. Antagonistas histamínicos. Diálise renal.

## ABSTRACT

**Introduction:** Uremic pruritus is common among dialysis patients. Effective treatments are not readily available. Early evidence with antihistamines and gabapentin indicate variable effects. **Objective:** To compare the efficacy and side effects of gabapentin and desloratadine in patients with dialysis pruritus. **Methods:** Prospective, open-label, cross-over clinical trial in 22 patients on chronic hemodialysis with sustained pruritus over a period of at least 60 days. After a one-week run-in period, we assigned patients to three weeks of either gabapentin 300 mg thrice weekly or desloratadine 5 mg thrice weekly. After a one-week washout period, each patient crossed-over to the alternate regimen for three more weeks. The primary endpoint of the study was the change in the visual analogue pruritus score (VAS). **Results:** Nineteen subjects completed the two treatment blocks and were available for analysis. VAS scores decreased with both treatments (5.95 to 4.6 with gabapentin, p = 0.07; 5.89 to 3.4 with desloratadine, p = 0.004), but only desloratadine reached statistical significance. There were no differences when comparing the final pruritus score with gabapentin and desloratadine (4.6 *versus* 3.4, p = 0.16) Excessive sedation was common with gabapentin. Desloratadine was well tolerated. **Conclusion:** Desloratadine provides significant relief of uremic pruritus compared with no therapy. gabapentin has marginal efficacy. Desloratadine is better tolerated than gabapentin.

**Keywords:** Pruritus. Histamine antagonists. Renal dialysis.

## Introduction

Pruritus is a common symptom in chronic hemodialysis patients, with significant impact on quality of life.[1,2] Despite improvements in dialytic technology, the incidence of uremic pruritus remains between 20-30%.[3,4] The pathophysiology of uremic pruritus is unknown, which limits the use of effective treatments. Most patients are treated with topical emollients, though the majority requires the addition of systemic therapy.[5] Some of the more frequently used drugs are oral antihistamines (including hydroxyzine, cetirizine, loratadine, desloratadine), gabapentin, ondansetron, thalidomide, naltrexone/nalbufine, UV light and topical tacrolimus.[6-12] Unfortunately, the results of different studies are not uniform and have methodological inconsistencies, so that the best treatment options are still uncertain.[13]

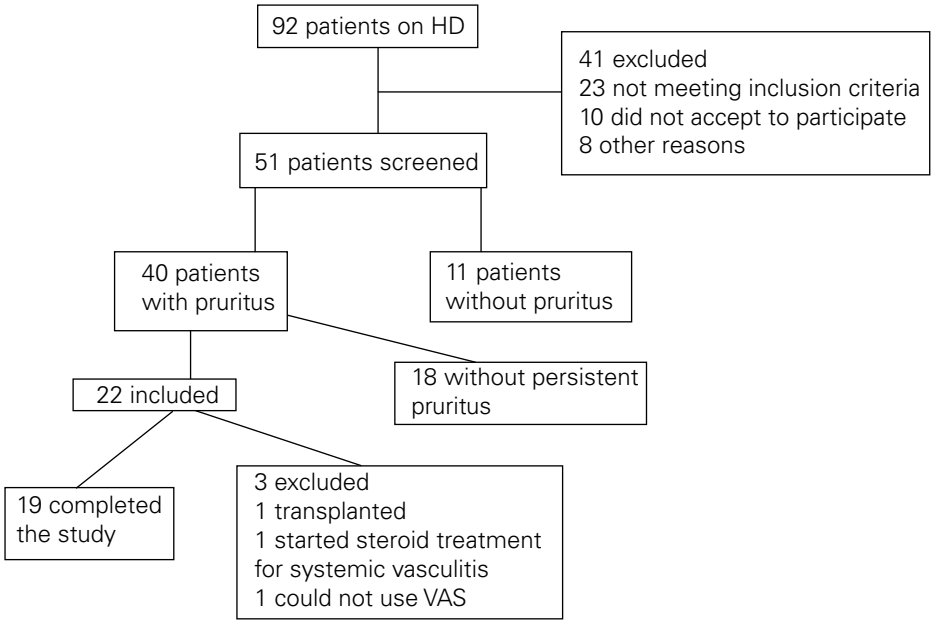
Given the widespread use of antihistamines for pruritic conditions, the use of gabapentin in patients with several sensory disturbances and the use of both drugs reported for dialysis pruritus, we conducted the present study comparing the efficacy and side effect profile of these agents.

## Methods

We conducted a prospective, open-label, cross-over study in chronic hemodialysis patients with uremic pruritus. Subjects were adults 18 years or older on stable hemodialysis for at least three months. Enrollment occurred between December 2007 and July 2008. In order to identify patients with persistent pruritus, we reviewed the records of 92 potentially eligible patients from our chronic hemodialysis unit (Figure 1). We excluded patients with chronic skin diseases (allergic, parasitic, infectious), chronic liver disease, systemic malignancies and those receiving chronic opiate therapy or corticosteroids. Of the 92 dialysis patients, 51 were eligible and willing to participate by answering to a pruritus assessment tool (Table 1) on two occasions ~60 days apart. "Persistent pruritus" was defined as pruritus of any intensity occurring three times a week throughout the initial 60 days of evaluation. After appropriate exclusions, 22 subjects started the intervention portion of the study. The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinski and its amendment. The local Ethics Committee approved the study, and all subjects provided written informed consent.

Patients received standard thrice weekly (four hours per session) bicarbonate-based hemodialysis with Fresenius 4008 machines and low-flux polysulfone membranes. Dializer reused was allowed. A 16 gauge needle, blood flow 350 mL/min and a dialyzer flux of 500 mL/min were used in all patients.

**Figure 1**. Flow chart of study participants




HD: Hemodialysis; VAS: Visual Analogue Scale.

### Assignment, interventions and measurements

Subjects who qualified for the study were taken off any antipruritic agents for a one-week run-in period (Figure 2). After this run-in/washout period, subjects were assigned to receive orally either desloratadine 5 mg (provided by Laboratorio Roemmers, Buenos Aires, Argentina) or gabapentin 300 mg (provided by Laboratorio Raffo, Buenos Aires, Argentina) three times a week. A physician study directly observed ingestion of the medications immediately after each dialysis session for a three-week period. Following another one-week washout period, subjects crossed over to the other treatment arm for three more weeks. We assigned the order of drug administration based on the dialysis schedule of each patient. The use of emollients or other coadyuvant treatment for pruritus was not allowed during the study.

We measured basic clinical and laboratory parameters at baseline. We applied the pruritus assessment tool (Table 1) at baseline and at the end of each treatment and washout periods. The investigator administering the questionnaire was blinded to the drug assignment.

### Statistical analysis

The primary endpoint of the study was the change in pruritus VAS during each treatment period. We considered an effect size of a two-unit difference in the final VAS between groups as clinically significant. To test this difference, and assuming a within-subject standard deviation of the VAS of ~2 units, 18 subjects were required to generate a power of 80% with a two-tailed alpha of 0.05. We performed intergroup comparisons using standard methods for repeated measures. For non-parametric data (such as visual analogue scores - VAS), we used the Wilcoxon test for paired measurements. We considered p values < 0.05 as statistically significant.

## Results

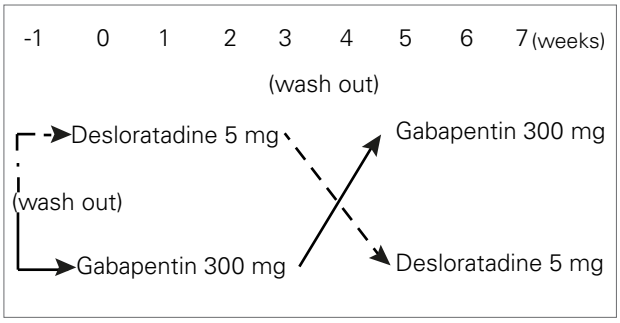
Twenty-two patients were assigned to the interventions. Of these, three did not complete the study (Figure 1), leaving 19 subjects for analysis. Table 2 describes the baseline patient characteristics. Baseline VAS scores for pruritus were 5.95 (range 4-8). Most patients had frequent (three or more times in a week), significant, and generalized pruritus.

Figure 3 shows the main results of the study. Both gabapentin and desloratadine resulted in decreased VAS scores compared with baseline, but only desloratadine reached statistical significance. There were

**Table 1** Pruritus assessment tool

| 1. Questions: |
|---|
| - History of pruritus (Do you usually complain about pruritus?) |
| - Frequency (number of episodes during a week) |
| - Localization (head, neck, arms, legs, abdomen, back) |
| - Time of day that appear |
| - Impact on quality of life (Does it affect on sleep, during activities, etc.) |
| - Solutions that you try during pruritus access (medications, other therapies) |
| 2. Intensity: VAS (Visual Analogue Scale) |
| 0 1 2 3 4 5 6 7 8 9 10 |

**Figure 2.** Treatment assignment scheme




no statistically significant differences between the two agents when comparing the final VAS for each group (4.6 *versus* 3.4, p = 0.16). Eleven of 19 patients (58%) experienced a relative decrease in VAS of least 50% while on desloratadine, whereas 5 of 19 (16%) had similar reductions while on gabapentin (p = 0.049, Fisher's exact test).

While receiving gabapentin, 9 of 19 subjects (47%) reported fatigue and somnolence, and 4 of these patients discontinued use of the drug due to excessive somnolence, all after the first dose. While receiving desloratadine, one subject discontinued treatment due to nervousness. No other adverse events were reported.

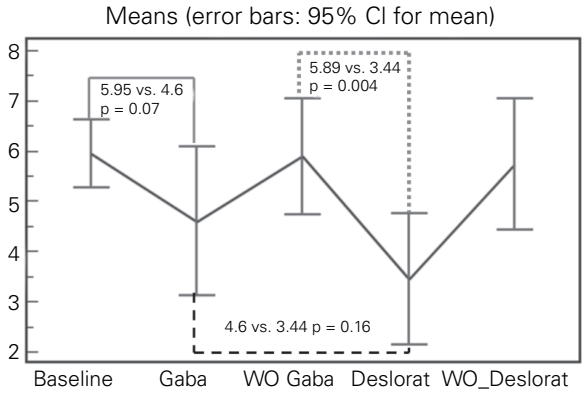
## Discussion

We have demonstrated that both gabapentin and desloratadine improve pruritus in dialysis patients compared with baseline (no therapy), but only desloratadine reached statistical significance. There were no significant differences observed between the two drugs. However, in our patient population, desloratadine was associated with fewer side effects than gabapentin. Therefore, our overall impression is that

**Table 2** Baseline patient characteristics (n = 19)

| |
|---|
| Age (years): 54 ± 18 |
| Time on HD (years): 4.9 ± 3.9 |
| Vascular access (%): |
| - AVF 84.2 |
| - Graft 10.5 |
| - Cuffed Catheter 5.2 |
| Laboratory test: |
| - Hematocrit (%) 32.5 ± 4.3 |
| - Creatinine (mg/dL) 9 ± 2.7 |
| - Urea (mg/dL) 133.1 ± 33.6 |
| - Phosphate (mg/dL) 5.1 ± 1.6 |
| - Calcium (mg/dL) 9.4 ± 1.2 |
| - Calcium x Phosphate 49.7 ± 17.9 |
| - Intact PTH (ng/dL) 529.4 ± 455 |
| - Protein catabolic rate 1.21 ± 0.3 |
| - Kt/V (single pool) 1.23 ± 0.3 |

**Figure 3.** Treatment results




Gaba: Gabapentin; WO: Wash out Gabapentin; Deslora: Desloratadine; WO_Deslorat: Wash out Desloratadine.

desloratadine is a preferable agent for the treatment of dialysis pruritus.

Dialysis pruritus is still a condition without effective treatment. It is probably caused by multiple mechanistic pathways, thus limiting the relative efficacy of any individual treatment options. This often leads to patient and physician frustration. Because antihistamines and gabapentin have been used in many studies,[6,14] we chose to compare these two classes directly.

Studies evaluating the efficacy of gabapentin demonstrated improvement in pruritus in about 80% of the patients.[16-18] Our results were not as impressive as those of other investigators. Razeghi *et al*. compared gabapentin with placebo and showed a reduction in pruritus score in the majority (73%) of the patients.[19] Similar observations were noted in three other studies (83-79-85%).[16-18] It is not entirely clear to us why our response rates were lower than those observed by others. Patient characteristics were relatively similar, and the doses used were similar to the studies of Gunal *et al*. (300 mg three times a week) and Naini *et al*. (400 mg two times a week).[17,18] All of these studies carried the intervention for four weeks rather than the three weeks in our study, but we have little reason to believe that this short period would have a significant additional effect on pruritus control.

To our knowledge, this is the first study using desloratadine for uremic pruritus.

Desloratadine is the major active metabolite of loratadine. The main difference between them is that desloratadine is a non-sedative antihistamine. However, the pharmacokinetic of desloratadine was less study than loratadine. Considering the studies with loratadine and the increase half life in patients with end-stage renal disease (ESRD), we used desloratadine in the same way to avoid possible adverse events in our study.[15] This long half life permitted us to give it at the end of each dialysis session, as well as Gabapentin, and assure that the patient received the treatment.

However, several other antihistamines have been evaluated with modest results.[6,14] Of particular relevance, the antihistamine loratadine has been evaluated in a trial comparing it with naltrexone.[14] In this two-week study, loratadine produced a minor effect on VAS (only one unit on average) that was not statistically significant.

Although most would argue that there are no clinically relevant differences between the two agents, our observations proved otherwise.

The frequent intolerance to gabapentin is perhaps the most significant finding from our study. Other studies with gabapentin in uremic pruritus have reported adverse event in many of the patients.[16-19] Sedation, dizziness and somnolence were the most common symptoms and all of them were observed after the first dose. Only in the study of Razeghi *et al*. two patients discontinued due to adverse events. These symptoms are in concordance with our observations, although in our study four patients discontinued. It is our substantiate impression that, although effective for symptom control, gabapentin should not be used unless other strategies, such as topical therapy with

emollients and oral use of antihistamines, have not been effective. It is possible that the excessive rates of sedation observed were due to our starting dose of 300 mg, higher than the used in some of the previous studies,[16,19] though others used this dose as well.[17,18] It may be advisable to start at a lower dose (e.g., 100 mg once daily, as in the Razeghi study) and progressively titrate as tolerated. Desloratadine, on the other hand, was well tolerated, as was loratadine in the study of Legroux-Crespel *et al*.[14]

Our study has several limitations. First and foremost, it was not placebo-controlled. Other studies in the field indicate minimal effects from placebo, so we believed it was not necessary to have a placebo group in our study. Second, it is possible that the three-week intervention period was insufficient to lead to maximal effects. Lastly, our sample size was not large enough to detect small differences in efficacy, possibly explaining the lack of statistical significance in the difference of achieved VAS and pruritus control between the two groups.

In conclusion, our study provides evidence in support of the use of both gabapentin and desloratadine as modestly effective treatments in uremic pruritus. The unfavorable side effect profile of gabapentin should limit its use as first line therapy. Further work is necessary in search of more effective treatments for uremic pruritus.

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