

Low-Dose Doxepin for Treatment of Pruritus in Patients on Hemodialysis

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Introduction. Pruritus is one of the frequent discomforting complications in patients with end-stage renal disease. We prospectively evaluated the effectiveness of doxepin, an H1-receptor antagonist of histamine, in patients with pruritus resistant to conventional treatment.

Materials and Methods. A randomized controlled trial with a crossover design was performed on 24 patients in whom other etiologic factors of pruritus had been ruled out. They were assigned into 2 groups and received either placebo or oral doxepin, 10 mg, twice a day for 1 week. After a 1-week washout period, the 2 groups were treated conversely. Subjective outcome was determined by asking the patients described their pruritus as completely improved, relatively improved, or remained unchanged/worsened.

Results. Complete resolution of pruritus was reported in 14 patients (58.3%) with doxepin and 2 (8.3%) with placebo ($P < .001$). Relative improvement was observed in 7 (29.2%) and 4 (16.7%), respectively. Overall, the improving effect of doxepin on pruritus was seen in 87.5% of the patients. Twelve patients (50.0%) complained of drowsiness that alleviated in all cases after 2 days in average. One patient refused to continue the treatment due to its sedative effect.

Conclusions. We suggest that doxepin, a tricyclic antidepressant with anti-H1 receptor effect, can help improve pruritus resistant to antihistamines in end-stage renal disease patients who undergo hemodialysis. A low dose of doxepin is safe while effective and its main adverse effect, drowsiness, is temporary and can be easily tolerated by the patients.

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INTRODUCTION

Pruritus is a common dermatologic complaint of patients with end-stage renal disease (ESRD), mostly not responding to dialysis. Almost 60% of patients on dialysis suffer from pruritus, of whom 80% do not benefit from conventional treatment.¹ This can lead to complications such as lichen simplex, keratotic papules, follicular hyperkeratosis, and prurigo modularis.²

Considering the high sensitivity to histamine and the elevation in serum levels of histamine in uremic pruritus patients, antihistaminic agents can improve the symptom without the elimination of the causal factors.³ Accordingly, we decided to investigate the effectiveness and safety of doxepin, a tricyclic antidepressant drug with a strong anti-H1 histaminic receptor effect, in patients on hemodialysis.

MATERIALS AND METHODS

A randomized double-blind study was designed in a crossover fashion at the dialysis center of Shaheed Labbafinejad Medical Center in Tehran, Iran. The study was approved by the ethics committee of the Urology and Nephrology Research Center. Of all the patients on hemodialysis who suffered from pruritus, the ones who met the following criteria were selected: hemodialysis, 3 times a week with a Kt/V > 1.2, serum calcium levels less than 11.5 mg/dL, serum phosphate levels less than 6.5 mg/dL, serum intact parathyroid hormone between 13.0 pg/mL and 66.0 pg/mL, serum aluminum between zero and 6 ng/mL, serum magnesium less than 2.6 mg/dL, and blood hemoglobin level greater than 10 mg/dL. The exclusion criteria were the administration of antipruritus drugs a week prior to the study and hemodialysis due to acute renal failure. Twenty-four patients were eligible to enroll in the study and provided informed consent. They were randomly assigned into groups 1 and 2. Doxepin, 10 mg, (Pakhshe Razi, Tehran, Iran) was placed in another capsule in order to provide placebo capsules similar in shape, size, and color. The prepared capsules were tested in a pharmaceutical laboratory without any conflict of interest to this study and it was confirmed that they were comparable to the original doxepin capsules in the time required to be digested and opened in the stomach. For a 1-week period, the patients in group 1 received doxepin with a dosage of 10 mg twice a day, and those in group 2 received placebo. Afterwards, preceded by another 1-week as a washout period (without antipruritus drugs or doxepin), the patients in group 1 received placebo and those in group 2 received doxepin with the same dose for 1 week. The patients and the physicians involving in their management were blind to the randomization. Response to the treatment was recorded as complete improvement (no more itching), relative improvement (reduction of the symptom), and no effect (symptom remained unchanged or worsened) based on the patients' subjective report. Also, the patients were monitored for complications in every dialysis session.

Data were analyzed by the SPSS software (Statistical Package for the Social Sciences, version 10.0, SPSS Inc, Chicago, Ill, USA) and the chi-square test and Fisher exact test were used to compare

proportional variables. A value for *P* value less than .05 was considered significant.

RESULTS

Of all the uremic patients with pruritus undergoing maintenance hemodialysis at our center, 24 met the criteria of inclusion in the study. One patient refused to complete the study due to its adverse effect, and thus, his symptom was treated as completely improved by placebo while remained unchanged by doxepin. Eleven of the patients (45.8%) were women and 13 (44.2%) were men and their mean age was 48.0 ± 5.6 years (range, 35 to 65 years).

In all of the enrolled patients, serum calcium was in a range between 7.4 mg/dL and 10.7 mg/dL; phosphorus, 4.2 mg/dL and 6.1 mg/dL; magnesium, 2 mg/dL and 2.5 mg/dL; serum intact parathyroid hormone, 13 pg/mL and 66 pg/mL; blood hemoglobin, 10 g/dL and 11 g/dL; and Kt/V, 1.2 and 1.5. Ten patients (41.7%) received erythropoietin weekly, but the others did not receive it regularly.

The Table outlines the results of doxepin administration reported by 24 patients. Complete improvement was achieved in 58.3% with doxepin, which was significantly higher compared to that with placebo ($P < .001$). Overall, doxepin was effective in 87.5% of the patients ($P < .001$).

Drowsiness was the main complaint reported by 12 out of 24 patients (50.0%), which was alleviated after an average of 2 days. Nonetheless, it caused 1 patient to refuse to continue drug administration.

Response to Treatment of Pruritus by Doxepin in Patients With End-Stage Renal Disease

Response to Treatment	Drug	
	Doxepin	Placebo
Complete improvement	14 (58.3)	1 (8.3)
Relative improvement	7 (29.2)	4 (16.7)
No effect	3 (12.5)	18 (75.0)

DISCUSSION

In the present study, we found a significant effectiveness of doxepin for the treatment of pruritus in ESRD patient receiving hemodialysis. The etiology of pruritus in ESRD has remained obscure and multiple underlying factors have been proposed in the literature.⁴ Antihistamines

are usually ineffective in patients with uremic pruritus.⁴ Doxepin has been attempted in many studies as a treatment for pruritus, but, to our best knowledge, not in ESRD patients. Greene and colleagues compared the effect of doxepin and diphenhydramine in the systemic form for the treatment of idiopathic urticaria. They used doxepin, 10 mg, 3 times a day, and recorded the subjective outcomes. Doxepin could completely remove the symptom in 43% of the patients while only 5% experienced improvement with diphenhydramine. The relative improvement by doxepin was also remarkable (74% versus 10%). However, they considered a short washout period (3 days) and the results might have been influenced by their previous treatment.⁵ Goldsobel and associates reported a high efficacy of doxepin in 16 patients with resistant chronic idiopathic urticaria in comparison with placebo. The most common adverse effect was drowsiness for the first 3 days.⁶ In the abovementioned study, no washout period was considered in the study design.

Doxepin was preferred by patients with urticaria in a randomized double-blind trial by Neittaanmaki and colleagues.⁷ In this study, doxepin was compared with cinnarizine, cyproheptadine, and hydroxyzine; 8 out of 9 patients found doxepin the most effective one, in the first trial. Drugs with antihistaminic activity may be helpful patients with symptoms associated to the role of histamine. Nonetheless, this role in the pathogenesis of uremic pruritus is a matter of controversy; Weisshaar and colleagues compared 11 hemodialysis patients with pruritus with 10 healthy controls. They showed that histamine and serotonin values were in the reference range in both groups and thus, antihistamines had marginal effect on pruritus.⁸ This can explain why Benchikhi and coworkers found that antihistamines—the first-line therapeutic agents in patients on dialysis—were not effective in 134 patients with pruritus.⁹ A study by Francos and associates, however, has supported the hypothesis that the activation of the mast cells contributes to the pruritus in uremic patients; venous plasma histamine and histaminase levels were high. Furthermore, they showed that histaminase activity reduced with hemodialysis, while histamine level remained high.¹⁰ Consequently, trying an agent with high anti-H1 receptor activity seems to be logical in hemodialysis patients.

In our study, doxepin was administered with a low dose which was still effective. Considering a proper washout period, the confounding effects of other antipruritus therapies was minimized; hence, the reduction in the severity of the symptom can be directly the result of using doxepin. On the other hand, most patients on dialysis also suffer from anxiety and depression, and the use of doxepin with its combination of properties is can be a good choice among the potential therapeutic agents for chronic pruritus.⁴

CONCLUSIONS

Doxepin, as an H1-receptor blocker, is an effective and safe choice not only in idiopathic pruritus, but also in uremic pruritus resistant to conventional treatments. However, further studies with larger sample sizes are warranted. We suggest a comparison of doxepin with other most effective drugs and objective outcome measurements.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Stahle-Backdahl M. Uremic pruritus. Clinical and experimental studies. *Acta Derm Venereol Suppl (Stockh)*. 1989;145:1-38.
2. Hurwitz RM. The evolution of perforating folliculitis in patients with chronic renal failure. *Am J Dermatopathol*. 1985;7:231-9.
3. Young AW Jr, Sweeney EW, David DS, et al. Dermatologic evaluation of pruritus in patients on hemodialysis. *N Y State J Med*. 1973;73:2670-4.
4. Greaves MW. Itch in systemic disease: therapeutic options. *Dermatol Ther*. 2005;18:323-7.
5. Greene SL, Reed CE, Schroeter AL. Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. *J Am Acad Dermatol*. 1985;12:669-75.
6. Goldsobel AB, Rohr AS, Siegel SC, et al. Efficacy of doxepin in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol*. 1986;78:867-73.
7. Neittaanmaki H, Myohanen T, Fraki JE. Comparison of cinnarizine, cyproheptadine, doxepin, and hydroxyzine in treatment of idiopathic cold urticaria: usefulness of doxepin. *J Am Acad Dermatol*. 1984;11:483-9.
8. Weisshaar E, Dunker N, Domrose U, Neumann KH, Gollnick H. Plasma serotonin and histamine levels in hemodialysis-related pruritus are not significantly influenced by 5-HT3 receptor blocker and antihistaminic therapy. *Clin Nephrol*. 2003;59:124-9.
9. Benchikhi H, Moussaid L, Doukaly O, Ramdani B, Zaid D, Lakhdar H. Hemodialysis-related pruritus. A study of 134

Moroccans. *Nephrologie*. 2003;24:127-31.

10. Francos GC, Kauh YC, Gittlen SD, et al. Elevated plasma histamine in chronic uremia. Effects of ketotifen on pruritus. *Int J Dermatol*. 1991;30:884-9.

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