κ-Opioid System in Uremic Pruritus: Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Studies

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Uremic pruritus is a very common and frustrating condition for both patients and clinicians because no treatment has been demonstrated to be effective in relieving the itch. In this report, nalfurafine, a new κ-opioid receptor agonist, was used to treat uremic pruritus in patients who were undergoing routine hemodialysis. Two multicenter, randomized, double-blind, placebo-controlled studies enrolled 144 patients with uremic pruritus to postdialysis intravenous treatment with either nalfurafine or placebo for 2 to 4 wk. A meta-analysis approach was used to assess the efficacy of nalfurafine. Statistically significant reductions in worst itching (P = 0.0212), itching intensity (P = 0.0410), and sleep disturbances (P = 0.0003) were noted in the nalfurafine group as compared with placebo. Improvements in itching (P = 0.0025) and excoriations (P = 0.0060) were noted for the nalfurafine-treated patients. Nalfurafine showed similar types and incidences of drug-related adverse events as did placebo. Nalfurafine was shown to be an effective and safe compound for use in this severely ill patient population.


Materials and Methods

Study Design and Treatments

Two multicenter, randomized, double-blind, placebo-controlled clinical studies were performed with the common objective of assessing the efficacy and the safety of nalfurafine, as compared with placebo, in the treatment of uremic pruritus. The inclusion and exclusion criteria and the evaluations, methods of evaluations, and times of evaluations were the same in both studies.

Patients were males and females who were at least 18 yr of age and undergoing routine hemodialysis secondary to ESRD and had severe, uncontrolled pruritus caused only by ESRD. Female patients were not of childbearing potential or were using an acceptable contraceptive method(s). They had normal hepatic function, and any concurrent diseases were stable, were not severe, and would not interfere with interpretations of the study results. All patients completed the “worst itching” visual analogue scale (VAS) at least 8 of 14 times during a 1-wk run-in period. Each patient had at least three “worst itching” VAS measurements during the run-in period of ≥50 mm and an average “worst itching” VAS of ≥25 mm. Excluded were female patients who were pregnant, were nursing, or wanted to become pregnant; patients whose pruritus occurred only during dialysis; and patients who had participated in a clinical trial or received an experimental drug within 30 d of trial start. Patients with a history of drug/alcohol abuse, allergy to opioids or other drug allergies, or a psychiatric disorder were excluded.

The first study (study 1) was a parallel-group design with the treatment lasting for 4 wk. Seventy-nine patients were randomly assigned in this study, and 74 completed the 4 wk of treatment. Before the run-in period (baseline), all anti-pruritic medications, except for topical agents, were discontinued for at least 7 d. After the run-in period in which it was documented that patients had pruritus that required treatment [itching uncontrolled by current medication(s)/treatment(s)], the patients were randomly assigned to receive nalfurafine 5 μg (n =
26) or placebo (n = 25) thrice weekly by intravenous infusion, immediately after completion of each of their hemodialysis (HD) sessions in 4 wk. A follow-up visit was performed 2 wk after administration of the final dose of study medication.

The second study (study 2) was a crossover design in which patients were randomly assigned 1:1 to receive for 2 wk an intravenous infusion of either nalfurafine 5 μg or placebo thrice weekly immediately after each of their HD sessions. Before randomization, patients underwent a 1-wk run-in period to determine their eligibility. At the completion of the first treatment period, patients underwent a 3-wk washout period followed by another 1-wk run-in period. Patients then were crossed over to the other study medication for an additional 2 wk of therapy. Thirty-four patients were randomly assigned to this study, and 31 completed the 4 wk of treatment.

The severity of pruritus and the treatment effectiveness were self-evaluated by the patients every 12 h during the run-in period and throughout the studies using a 100-mm VAS to measure the “worst itching” during the previous 12 h as the primary endpoint. At the left end of the scale (0 mm) was “no itching” and the right end (100 mm) represented “worst itching ever” with the patient making a vertical line between “0” and “100” to denote the severity of itching. Secondary efficacy end points were (1) patient responders as defined by a reduction from run-in of at least 50% in “worst itching” VAS, (2) itching intensity assessed each evening using a five-point categorical scale ranging from 1 (no itching) to 5 (intolerable itching), and (3) ability to sleep during the night assessed each morning using a five-point categorical scale ranging from 1 (no itching) to 5 (cannot sleep because of itching).

In addition, the investigators assessed (1) the itching intensity of the patients by direct questioning of the patients using the same five-point categorical scale used by the patients and compared the efficacy of the study medication using a three-point scale (same, better, worse compared with run-in) performed at the end of each week of treatment and (2) the number of excoriations on the body during run-in and after each 2 wk of therapy and compared these values with those at run-in using a three-point scale (same, better, worse).

Each dose of double-blind study medication in both studies was administered as an intravenous infusion at a rate of 2 ml/min for 5 min using an infusion pump. All doses were administered immediately after conclusion of each HD session.

**Ethics**

The studies were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and its amendment. Both protocols and the representative informed consent forms and patient information sheets underwent review and received approval by the representative ethics committees. All patients were informed and had questions answered by the investigators at each study site before they provided written informed consent. All patients provided their written informed consent before having any study-related procedures performed.

**Statistical Analyses**

The primary end point for each of the clinical trials was reduction in mean “worst itching” VAS from run-in to the end of week 4 (study 1) and week 2 (study 2). This end point was prespecified before the initiation of either trial. Likewise, the primary end point for the meta-analysis was reduction in mean “worst itching” VAS from run-in to week 2.

All patients who had received at least one dose of study medication and had at least one assessable “worst itching” VAS measurement were included in a FAS data set. With the intention to select comparable data from the two studies, only the data from the nalfurafine 5 μg and the placebo groups were used in these analyses because it allowed pooling of the same dose groups, thus increasing the sample sizes. Using only the data from the first 2 wk of treatment in study 1 and the first 2-wk treatment period in study 2 was considered appropriate because of concerns of the drug carryover effects and regression to the mean. For any missing data, the last observation carried forward approach was used.

The primary end point (worst itching VAS) was analyzed using an analysis of covariance model. Treatment, study, and run-in values were used as factors in the model. This corresponds to the model used in the individual studies, stratified by study. For the weighted analysis of “worst itching” VAS in study 1 + period 1 study 2 and study 1 + study 2, the DerSimonian-Laird method (16,17), a random-effects model, was used. The DerSimonian estimates were equal to ordinary fixed-effects model estimates because the heterogeneity parameter τ was found to be zero.

For the secondary efficacy variables, patients’ assessment of itching intensity and sleep disturbances were analyzed using analysis of covariance models, with treatment, study, and run-in value as factors. For analysis purposes, these variables were reclassified as follows: 1, nondisturbing itching (originally recorded as “0, no itching” or “1, tolerable without scratching”), and 0, disturbing itching (originally recorded as categories 2 through 5 above), or as 1, sound sleep (originally recorded as “0, no itching” or “1, sound sleep with slight itch on retiring”), and 0, sleep disturbed (originally recorded as categories 2 through 5 above).

The sum of the reclassified itching intensity or sleep disturbance variables was used to estimate the number of days with nondisturbing itching or to estimate the number of nights with sound sleep within a study week, respectively. The change from run-in was not used for hypothesis testing.

Investigators’ assessments of improvement in itching and excoriation and the proportion of responders in each treatment group were analyzed using the Cochran-Mantel-Haenszel test stratified for study (with modified ridit scores). An overall comparison was performed using Fisher exact test.

Two-sided P < 0.05 was considered to indicate statistical significance. Statistical calculations were performed with SAS software (version 8.2; SAS Institute, Cary, NC).

**Results**

**Efficacy**

Using the complete study 1 + study 2 data sets, 86 patients were treated with nalfurafine, and 58 patients received placebo. In study 1, 26 patients were randomly assigned to nalfurafine 5 μg, and 25 received with placebo. Sixteen patients were randomly assigned to nalfurafine 5 μg and 18 received placebo in the first period of study 2. A total of 42 patients received nalfurafine 5 μg as the first medication for 2 wk, and 43 patients started with placebo in the study 1 + period 1 study 2 analysis. All demographic and clinical characteristics including the durations of renal disease, dialysis, and pruritus in each study were comparable.

Evaluation of the mean “worst itching” VAS from the study 1 + period 1 study 2 analysis demonstrated that nalfurafine reduced the mean “worst itching” VAS from run-in statistically significantly more than placebo (weighted mean difference 9.53 mm; 95% confidence interval 1.42 to 17.64 mm; P = 0.0212;
Figure 1). This is similar to the results from the individual studies (Tables 1 and 2). Using data from both treatment periods in the crossover study as a sensitivity analysis, study 1 + study 2, the reduction of the mean “worst itching” VAS also reached statistical significance (weighted mean difference 7.29 mm; 95% confidence interval 0.17 to 14.4 mm; : 0.0447; Figure 1).

Responders were patients with at least a 50% decrease from baseline in “worst itching” VAS. At the 2-wk time point (study 1 + period 1 study 2), 15 (36%) of the nalfurafine patients were responders as compared with 6 (14%) in the placebo group (: 0.0226). When several variables (age, gender, height, weight, smoking status, and alcohol intake) were evaluated to determine a characteristic(s) that could be predictive of a responder, none was identified.

For patients’ assessment, both number of days with nondisturbing itching and number of nights with sound sleep were statistically significantly different between groups at week 2, in favor of nalfurafine (: 0.0010 and : 0.0003, respectively; Table 3). The number of days with nondisturbing itching in the nalfurafine group improved from 0.6 d/wk at the run-in period to 2.2 and 2.8 d at week 1 and week 2, respectively. Also, the number of nights with sound sleep in the nalfurafine group improved from 1.7 nights/wk at the run-in period to 3.4 and 4.3 nights at week 1 and week 2, respectively.

The investigators’ assessment of itching demonstrated a statistically significant improvement (: 0.0025) in favor of nalfurafine. The nalfurafine group also had a statistically significant improvement (: 0.0060) in excoriations, as judged by the investigators (Table 4).

Using the meta-analysis approach, it was demonstrated that nalfurafine produced a statistically significantly greater improvement in the “worst itching” VAS as compared with placebo after 2 wk of therapy. When the reduction of “worst itching” VAS over 4 wk of treatment (study 1) was reviewed, a continued reduction in VAS occurred for the next 2 wk for nalfurafine (21.5 mm at 2 wk and 25.8 mm at 4 wk). Although statistical significance was not demonstrated in this study, the data suggested that nalfurafine was clinically effective for at least 4 wk (Table 1).

**Table 1.** Summary of “worst itching” VAS (mm) at the end of weeks 2 and 4 in study 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalfurafine, 5 µg</td>
<td>Run-in</td>
<td>26</td>
<td>65.3</td>
<td>15.2</td>
</tr>
<tr>
<td></td>
<td>Week 2</td>
<td>26</td>
<td>44.9</td>
<td>26.5</td>
</tr>
<tr>
<td></td>
<td>Week 4</td>
<td>26</td>
<td>40.3</td>
<td>27.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>Run-in</td>
<td>25</td>
<td>65.3</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>Week 2</td>
<td>25</td>
<td>55.5</td>
<td>21.5</td>
</tr>
<tr>
<td></td>
<td>Week 4</td>
<td>25</td>
<td>52.6</td>
<td>24.0</td>
</tr>
</tbody>
</table>

*aVAS, visual analog scale.

**Table 2.** Summary of “worst itching” VAS (mm) at the end of week 2 in period 1 in study 2

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalfurafine, placebo</td>
<td>Run-in</td>
<td>16</td>
<td>63.6</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td>Period 1</td>
<td>16</td>
<td>41.5</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>(nalfurafine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo, nalfurafine</td>
<td>Run-in</td>
<td>18</td>
<td>61.9</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>Period 1</td>
<td>18</td>
<td>48.4</td>
<td>19.1</td>
</tr>
<tr>
<td></td>
<td>(placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Mean changes from run-in to week 2 in number of days with nondisturbing itching and number of nights with sound sleep: Study 1 + period 1 study 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Score at Run-in ± SD</th>
<th>Mean Score at Week 2 ± SD</th>
<th>Mean Change ± SD</th>
<th>P Value (95% CI)a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of days/wk with nondisturbing itching</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nalfurafine (n = 42)</td>
<td>0.6 ± 1.1</td>
<td>2.8 ± 2.6</td>
<td>2.2 ± 2.2</td>
<td>0.0410 (0.04 to 1.79)</td>
</tr>
<tr>
<td>placebo (n = 43)</td>
<td>0.8 ± 1.2</td>
<td>2.1 ± 2.5</td>
<td>1.4 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>No. of nights/wk with sound sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nalfurafine (n = 42)</td>
<td>1.7 ± 2.3</td>
<td>4.3 ± 2.4</td>
<td>2.5 ± 2.0</td>
<td>0.0003 (0.72 to 2.47)</td>
</tr>
<tr>
<td>placebo (n = 43)</td>
<td>2.1 ± 2.4</td>
<td>3.1 ± 2.6</td>
<td>0.9 ± 2.1</td>
<td></td>
</tr>
</tbody>
</table>

aCI, confidence interval.
bCompared with placebo.

Table 4. Summary statistics of investigators’ assessment of excoriations: Study 1 + period 1 study 2a

<table>
<thead>
<tr>
<th>Excoriations</th>
<th>Better</th>
<th>Same</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nalfurafine (n = 24b)</td>
<td>12</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>placebo (n = 24b)</td>
<td>3</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Period 1 study 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nalfurafine (n = 16)</td>
<td>15</td>
<td>94</td>
<td>1</td>
</tr>
<tr>
<td>placebo (n = 16b)</td>
<td>12</td>
<td>75</td>
<td>4</td>
</tr>
<tr>
<td>Study 1 + period 1 study 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nalfurafine (n = 40)</td>
<td>27</td>
<td>68</td>
<td>13</td>
</tr>
<tr>
<td>placebo (n = 40)</td>
<td>15</td>
<td>38</td>
<td>24</td>
</tr>
</tbody>
</table>

aP = 0.0060, Cochran-Mantel-Haenszel test stratified for study, using modified ridit scores, compared with placebo.
bTwo patients were withdrawn prematurely and not included in investigators’ assessment of itching.
°One patient was withdrawn prematurely and not included in investigators’ assessment of itching.

Safety

Evaluation of the safety profiles from these two studies assisted in assessment of the clinical utility of nalfurafine. In study 1, the incidence of drug-related adverse events (ADR), as judged by the investigators, was similar between nalfurafine 5 µg and placebo groups: 17 (65%) of 26 and 13 (52%) of 25, respectively. The most common ADR associated with nalfurafine were headache and nausea in three patients each and insomnia, vertigo, and vomiting in two patients each. With the exception of one case each of severe headache and insomnia, all of these ADR were mild to moderate in intensity and resolved. Only one patient, who had moderate nausea and vomiting, had therapy discontinued. Two (8%) patients in the nalfurafine 5 µg group and six (24%) patients in the placebo group reported at least one serious adverse event (SAE), but none of the SAE was considered to be drug related.

In study 2, the incidence of ADR was similar between the nalfurafine 5 µg and placebo groups: 2 (13%) of 16 and 2 (11%) of 18 patients, respectively. The most common ADR associated with nalfurafine were vertigo (one patient) and elevations of aspartate aminotransferase and alanine transaminase (one patient). All of these ADR were mild and resolved, and treatment was not discontinued. Three patients who were administered nalfurafine had an SAE and three on placebo recorded an SAE, but none of the SAE was considered to be drug related. In addition, there was no difference of withdrawal rates between the active treatment groups and placebo groups in both studies.

Discussion

To date, no treatments have demonstrated efficacy for uremic pruritus in a rigorously designed (randomized, double-blind, placebo-controlled) and carried out clinical study. On the basis of the data presented, it seems that nalfurafine, a κ-opioid receptor agonist, could be the first agent to have demonstrated a statistically significant efficacy over placebo for this condition. Efficacy (using the “worst itching” VAS) was confirmed in a recent study (data not shown) that used nalfurafine in patients who had uremic pruritus and were undergoing routine hemodialysis.

This meta-analysis should be regarded as a complement to the analyses of the pivotal study 1 and study 2, because the results were consistent for all analyses (Figure 1). In this very disturbing condition, an increase of attention and the sensation of being treated could be associated with subjective improvement (the Bergstrom effect [18]). Even so, the observed strong placebo effect was overridden by nalfurafine, which demonstrates the potent therapeutic effect of this medication.

That nalfurafine can reduce the itching associated with uremic pruritus suggests that opioid receptors may play an important role in the generation and maintenance of itching in this patient population. μ-Opioid receptor agonists elicit itching from their central nervous system actions (13,19), and this activity may be due to disinhibition of the central itch response that occurs as a result of their antinociceptive action (20). κ-Agonists have been shown to block the itching response of morphine through a central effect (13,21) while maintaining or enhancing morphine-induced antinociception. This anti-pruritic effect may be due to a direct effect in one or more areas of the brain and/or a positive feedback from the skin at the level of the spinal cord.
The itching of uremic pruritus may be caused by another pruritogen, substance P. This chemical has been shown to induce scratching in mice, with and without mast cells (14). Antihistamines were not effective in relieving the scratching in either setting. These findings suggest that substance P can be a possible cause of antihistamine-resistant pruritus. Nalfurafine has been shown to inhibit scratching in this model. This effect was reversed when nor-binaltorphimine, a specific κ-receptor antagonist, was administered, demonstrating that the anti-pruritic effect of nalfurafine was mediated via the κ-receptor (13,14).

Kumagai et al. (22) showed that the itch of uremic pruritus may be related to an imbalance of endogenous opioids. In their work, hemodialysis patients had increased ratios of β-endorphin/dynorphin A in serum, as compared with healthy volunteers, and this ratio increased with the severity of itching. Because β-endorphin is a µ-receptor agonist and dynorphin A is a κ-receptor agonist, it is suggestive that this imbalance can result in overactivity of the µ-opioid receptor and induce pruritus. In support of this imbalance hypothesis, Odou et al. (23) demonstrated a correlation between pruritus intensity and naltrrexone sensitivity in patients with uremic pruritus.

An explanation for the antagonistic actions of the µ- and κ-opioid systems is that although both receptors mediate their action in the same cellular manner, they are located in different types of neurons with direct connections to each other to elicit their inhibitory/excitatory interactions (24). Because these different receptors interact and the µ-receptor opioid system seems to play a major role in the pathophysiology of uremic pruritus, it seems reasonable that a selective κ-agonist, such as nalfurafine, would demonstrate effectiveness in the treatment of central itching, especially uremic pruritus.

Evaluation of the adverse events from these two trials demonstrates nalfurafine to be well tolerated in the clinical arena. The main events seem to be mediated by the central nervous system (headache, vertigo, and insomnia) and the gastrointestinal system (nausea and vomiting). As all of these adverse events were transient and resolved, this indicates that nalfurafine is a safe agent. Neither addiction nor symptoms of withdrawal were noted in these patients and has been confirmed with studies in animals. Nalfurafine seems to be both an effective and a safe agent to be used in the treatment of uremic pruritus in ESRD patients who are undergoing routine hemodialysis.

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Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/