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Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a Phase III, randomized, double-blind, placebo-controlled study

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Abstract

Background. Pruritus in haemodialysis patients is an intractable disease and substantially impairs their quality of life. Based on the results of our earlier clinical study, we hypothesized that the μ-(mu) opioid system is itch-inducible, whereas the κ (kappa) system is itch-suppressive.

Methods. The efficacy and safety of nalfurafine hydrochloride (a novel κ-receptor agonist) were prospectively investigated by randomly (1:1:1) administering 5 or 2.5 μg of the drug or a placebo orally for 14 days using a double-blind design in 337 haemodialysis patients with itch that was resistant to currently available treatments, such as antihistamines.

Results. The mean decrease in the visual analogue scale (VAS) from baseline, the study's primary endpoint, was significantly larger in the 5-μg nalfurafine hydrochloride group (n = 114) than in the placebo group (n = 111, P = 0.0002, one-sided test at 2.5% significance level). The decrease in the VAS in the 2.5-μg group (n = 112) was also significantly larger than that in the placebo group (P = 0.0001). The inci-

dence of adverse drug reactions (ADRs) was 35.1% in the 5-μg group, 25.0% in the 2.5-μg group and 16.2% in the placebo group. Moderate to severe ADRs were observed in 10 of the 226 patients. The most common ADR was insomnia (sleep disturbance), seen in 24 of the 226 nalfurafine patients.

Conclusions. This Phase III, randomized, double-blind, placebo-controlled, parallel-group, prospective study based on VAS evaluations clearly showed that orally taken nalfurafine hydrochloride effectively reduced itches that were otherwise refractory to currently available treatments in maintenance haemodialysis patients, with few significant ADRs. This novel drug was officially approved for clinical use in January 2009 by the Ministry of Health, Labour and Welfare of Japan.

Keywords: itch; κ-receptor agonist; nalfurafine hydrochloride; randomized controlled study; visual analogue scale

Introduction

Pruritus (itch) is defined as an unpleasant sensation that elicits the desire to scratch [1]. Pruritus caused by a systemic disorder involves an abnormality in the control mechanisms of itch sensation in the brain and is frequently refractory to currently available antipruritic drugs [2–5]. Uraemic pruritus occurs with an incidence of 42% in haemodialysis patients, and a subgroup of patients with itch who did not respond to conventional treatments was reported by Dialysis Outcomes and Practice Pattern Study (DOPPS) [6]. The DOPPS report and a Japanese report assessing 1773 haemodialysis patients with itch showed that uraemic itch induces depression, sleep disturbance and increased mortality [6,7]. Since antihistamines are only effective in some haemodialysis patients, a breakthrough is needed in terms of understanding the pathophysiology and treatment of this debilitating disease.

The opioid system has been considered as a cause of itch, since μ-opioid receptor agonists, such as morphine, induce severe itch in humans [1,3]. Although naltrexone, a μ-receptor antagonist, given orally for a week was reported to reduce the uraemic itch in 15 haemodialysis patients [8], another well designed study did not confirm that naltrexone has any antipruritic effect for uraemic itch [9]. Regarding the κ-opioid system, continuous epidural infusion of butorphanol (a partial κ agonist) for 24 h decreased pruritus due to epidural morphine in postoperative children [10]. Dawn and Yosipovitch [11] reported that intranasal butorphanol is successful for reducing intractable chronic itch due to prurigo nodularis, primary biliary cirrhosis, idiopathic elderly pruritus and non-Hodgkin's lymphoma.

We previously reported that the ratio of endogenous serum concentration of β-endorphin/dynorphin-A (the ratio of μ agonist/κ agonist) increased in proportion to the itch intensity in 37 haemodialysis patients complaining itch [12]. Furthermore, neuroscience research has shown that activation of κ receptors exerts inhibitory actions on μ receptor-mediated actions in the central nervous system (CNS) [13]. Therefore, we hypothesized that the endogenous μ-opioid system would be itch-inducible, whereas the κ system would be itch-suppressive.

Nalfurafine hydrochloride (TRK-820; Toray Industries, Inc, Kamakura and Urayasu, Japan; (2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide monohydrochloride) has been shown to be a selective κ-opioid receptor agonist based on *in vitro* receptor binding [14] and receptor activity studies [15]. Nalfurafine hydrochloride exhibits a broad range of antipruritic effects in both antihistamine-effective and -ineffective models of itch in monkeys and mice [16,17]. Three excellent reviews [3–5] have stated that this novel drug is expected to be effective for the treatment of uraemic pruritus resistant to conventional drugs. In randomized controlled studies, Wikström *et al.* [18] reported that nalfurafine administered intravenously after haemodialysis three times a week significantly reduced the itch intensity in 144 patients.

In the present report, we performed a prospective, Phase III, randomized, placebo-controlled, double-blind, parallel-group comparative study to examine the efficacy and safety of two doses of daily oral nalfurafine hydrochloride for the treatment of intractable pruritus in 337 haemodialysis patients. Changes in visual analogue scale (VAS) were compared between the nalfurafine and the placebo groups, as the primary endpoint.

Subjects and methods

Patients

This study enrolled patients on haemodialysis who were ≥20 years of age at the time of the provision of consent for this study and were regularly undergoing haemodialysis three times a week. To be eligible, all patients also had to have 'pruritus resistant to currently available treatments', defined as pruritus not responding adequately to systemic treatment (with oral or injectable prescription antihistamines or anti-allergy drugs) administered for 2 weeks or longer, nor to local treatment (with prescription drugs approved for the treatment of pruritus or moisturizing agents prescribed by physicians) during a 1-year period prior to the provision of consent for this study. We obtained written informed consent from every patient. The study protocol is in accord with the Helsinki declaration of 2000. The study protocol was approved by an internal review board at each haemodialysis clinic that participated in the study.

Measurement of itch

Itch severity was measured by the patients using VAS. We used VAS consisting of a 100-mm horizontal line with no scale markings. The patients were asked to mark the intensity of their itch on the scale, with strongest possible itch marked at the right end of the line (100 mm) and no itch marked at the left end (0 mm) [19]. VAS has been considered valuable to use as a quantified index of subjective sensation such as pain and itch. The patients were asked to mark the VAS value to record the worst degree of itch experienced during the previous 12 h twice a day (once in the morning and once in the evening) throughout the study period (for 36 days).

Study design

This study has a Phase III, multi-centre, randomized, double-blind, parallel-group comparative design in which three groups were treated with nalfurafine hydrochloride (5 or 2.5 μg) or a placebo. Patients continued the antipruritic drug treatment at the same dosage and administration schedule as used at baseline throughout the study.

During the last 7 days of the 14-day pre-observation period, the effects of the basic conventional therapy for itch were assessed by the patients

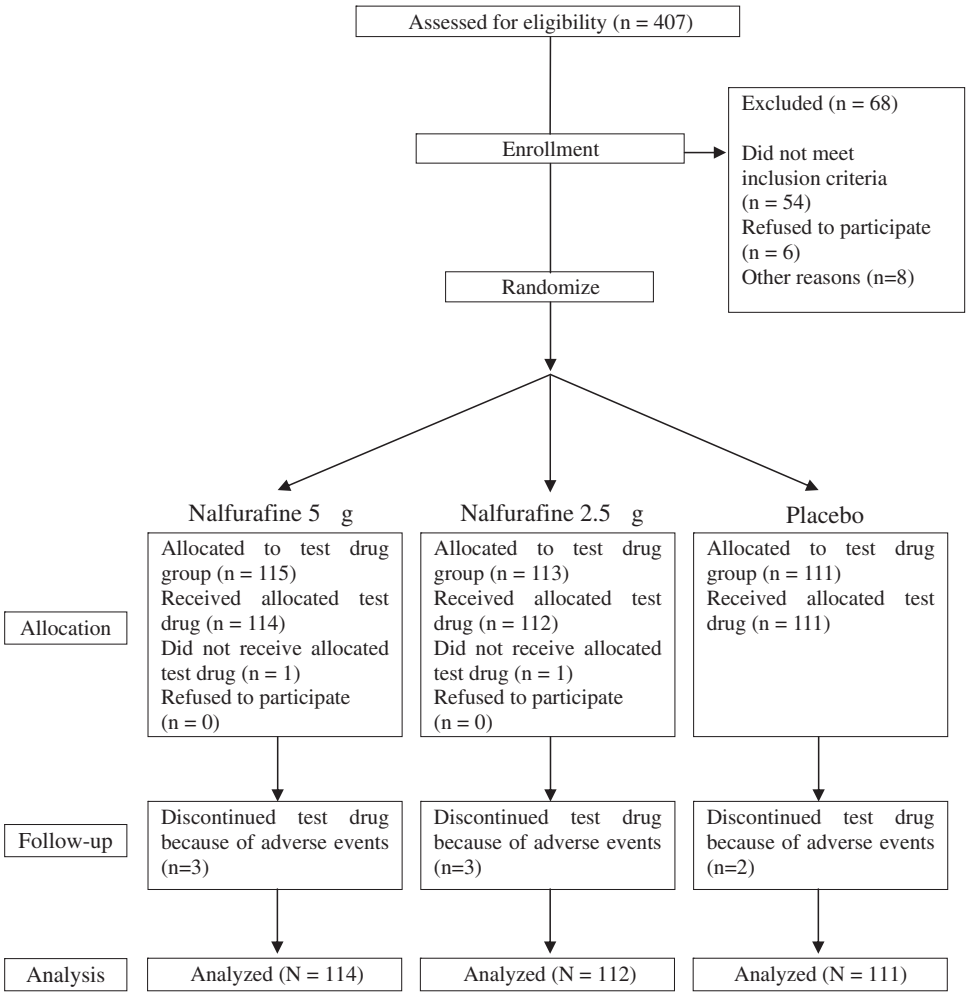

Fig. 1. Flow diagram of the progress through this randomized trial.

using the VAS value. Only patients who met all of the following criteria were enrolled: (i) VAS values were recorded a sufficient number of times [VAS values (both morning and evening) recorded on ≥5 days], (ii) mean morning or evening VAS value (whichever is larger) was ≥50 mm and (iii) daytime or night-time VAS value (whichever is larger) was ≥20 mm on more than 5 days during the last 7 days of the pre-observation period.

Those patients who met the above criteria were randomized 1:1:1 to receive 5 μg, 2.5 μg nalfurafine or a placebo using a variable size permuted block design stratified by centre. The patients took the soft capsules containing the drug or placebo once daily after supper for 14 days.

An 8-day post-observation period followed the 14-day treatment period. Throughout the study, the concomitant use of other opioids and phototherapy intended to treat pruritus was prohibited. Hypnotics, antidepressants, antipsychotics, antiepiletics and anxiolytics that were likely to affect itch were administered at a consistent dosage and via the normal method of administration throughout the study, as were the antipruritic drugs administered for basic therapy.

Change in VAS value (Primary Endpoint)

Using all the VAS values both in the morning and evening, the mean VAS values were calculated for the last 7 days of the pre-observation period, the first and latter 7 days of the treatment period and the 8-day post-observation period. Using the mean VAS value for the last 7 days of the pre-observation period as a baseline, the decrease in the mean VAS value from the baseline during each subsequent period was assessed as the change in the VAS value. The primary endpoint was defined as the change from the mean VAS value of the last 7 days of the pre-observation period and the mean VAS value of the latter 7 days of the treatment period.

Statistical analysis

The sample size was set at 100 patients per group by assuming an expected difference of 10.0 mm [with a common standard deviation (SD) of 25 mm] in the change in VAS values between the 5-μg nalfurafine hydrochloride and the placebo groups based on the mean VAS changes and SDs observed between these two groups in preceding clinical studies, with a one-sided significance level of 2.5% and a statistical power of 80%. The full analysis set (FAS), defined as all patients who were randomized and received at least one dose of study drug and were as close as possible to the intention-to-treat ideal, was chosen for examining the primary end point.

The change in the mean VAS values was used as the primary endpoint. The overall alpha (one-sided type I) error was controlled at the 0.025 level using a closed, sequence approach. The hierarchical order for testing the null hypotheses was pre-specified in the protocol. That is, the effect of nalfurafine hydrochloride 5 μg was compared to that of placebo at the first step of the procedure. Only if the first step was statistically significant, the effect of nalfurafine hydrochloride 2.5 μg was compared to placebo.

In both steps, intergroup comparisons were performed using an analysis of covariance (ANCOVA) with the change in the VAS values as a criterion variable and the mean VAS for the last 7 days of the pre-observation period as a covariate. The significance level was 2.5% (one-sided), and the two-sided 95% confidence interval (CI) was determined for the intergroup difference in the mean VAS values.

Adverse events and adverse drug reactions (ADRs) were tabulated for each treatment group in accordance with the system organ class and preferred terms of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Medical Dictionary for Regulatory Activities/J (MedDRA/J, Ver. 9.0). The adverse events and ADRs were then classified according to se-

Table 1. Patient background factors

Background factors		5-μg group (n = 114)	2.5-μg group (n = 112)	Placebo group (n = 111)
Sex	Male	93 (81.6%)	85 (75.9%)	89 (80.2%)
	Female	21 (18.4%)	27 (24.1%)	22 (19.8%)
Age (year)	Mean ± SD	59.6 ± 11.5	61.0 ± 11.4	59.6 ± 11.8
Weight (kg)	Mean ± SD	57.6 ± 10.7	56.9 ± 11.2	59.1 ± 10.4
Mean VAS value (mm) in the pre-observation period (last 7 days)	Mean ± SD	65 ± 14	69 ± 14	65 ± 14
Use of topical agents	Yes	23 (20.2%)	26 (23.2%)	26 (23.4%)
Use of oral antihistamines	Yes	23 (20.2%)	32 (28.6%)	26 (23.4%)
Use of antihistamine injection	Yes	6 (5.3%)	7 (6.3%)	6 (5.4%)
Use of oral anti-allergy drugs	Yes	68 (59.6%)	74 (66.1%)	75 (67.6%)
Use of anti-allergy drug injection	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
Use of hypnotics or anxiolytics	Yes	40 (35.1%)	49 (43.8%)	35 (31.5%)
Use of antiepileptics	Yes	6 (5.3%)	3 (2.7%)	3 (2.7%)
Use of antipsychotics or antidepressants	Yes	19 (16.7%)	19 (17.0%)	15 (13.5%)

Table 2. Changes in VAS values between the latter 7 days of treatment and pre-observation period

		Least-squares mean of VAS change		Difference from placebo group	
Treatment group	n	Point estimate	95% CI	Point estimate	95% CI for the difference
Nalfurafine 5-μg group	114	22	[19, 25]	9	[4, 14]
Placebo group	111	13	[10, 17]	P = 0.0002	
Nalfurafine 2.5-μg group	112	23	[19, 26]	10	[4, 14]
Placebo group	111	13	[9, 16]	P = 0.0001	

One-sided test at 2.5% significance level (Analysis population: FAS).

verity, seriousness and causal relationship to the study drug. Intergroup comparisons were conducted using two-sided 95% CIs for the risk ratio, risk difference and related variables.

We defined grade of insomnia as follows: mild, insomnia that did not interfere with usual activity and easily tolerated; moderate, insomnia that interfered with usual activity; and severe, insomnia that made incapable to do usual activity.

Results

Study population

The study was conducted at 73 centres throughout Japan, and 407 haemodialysis patients with severe itch were assessed for eligibility (Figure 1). Of these patients, 68 patients withdrew from the study or proved to be ineligible for formal registration. Of the 339 patients formally registered in the study, the participation of two patients was discontinued because these patients did not receive the study capsules.

Patient background factors are presented in Table 1. The three groups had similar background factors. A total of 337 patients received the study drugs in the study: 114 patients (111 patients completed treatment) in 5-μg nalfurafine group, 112 (109 completed treatment) in 2.5-μg nalfurafine group and 111 (109 completed treatment) in the placebo group. The percentage of patients who completed the study was 97.6%.

Decreases in VAS values

In the intergroup comparison in step I, the mean change in the VAS values between the latter 7 days of treatment period and pre-observation period was 22 mm in the 5-μg nalfurafine group and 13 mm in the placebo group (upper half of Table 2). The difference of 9 mm between the two groups was statistically significant with a one-sided test at 2.5% significance level (P = 0.0002).

In the subsequent intergroup comparison in step II (lower half of Table 2), the change in the VAS values was 23 mm in the 2.5-μg nalfurafine group and 13 mm in the placebo group, with a statistically significant difference of 10 mm with a one-sided test at 2.5% significance level (P = 0.0001).

Thirty seven of 114 haemodialysis patients in the 5-μg nalfurafine group and 32 of 112 patients in the 2.5-μg nalfurafine group showed a significant response (50% or more reduction of VAS values) in contrast to 19 of 111 patients in the placebo group showing the significant response.

As shown in Figure 2, pooled data of all morning and evening VAS values showed that, in the 5-μg nalfurafine group, decreases in the VAS values (mean = 16 with 95% confidence interval (CI) [13, 18] during the first 7 days of the treatment period and mean = 22 with 95% CI [18, 26] during the latter 7 days of the treatment period) were significantly larger than those in the placebo group (mean = 8 with 95% CI [6, 11] and mean = 13 with 95% CI [10, 16], respectively). In the 2.5-μg nalfurafine group, decreases in the VAS values (mean = 16 with 95% CI [13, 19] during the first 7 days of the treatment period and mean = 23 with 95% CI [19, 27] during the latter 7 days of the treatment period) were also significantly larger than those in the placebo group.

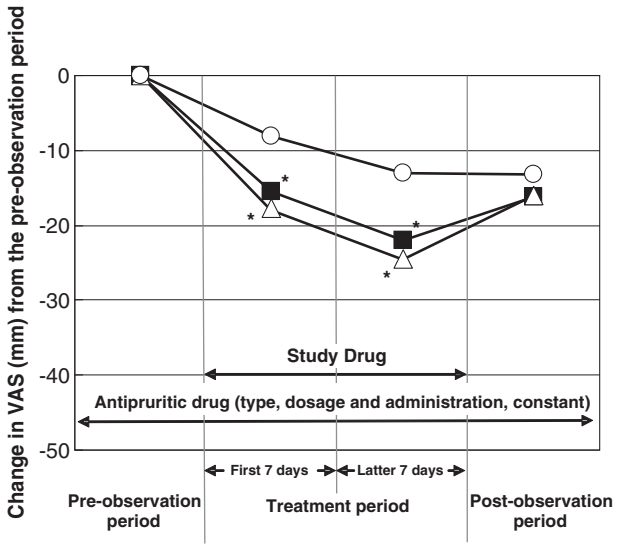

Fig. 2. Changes in VAS values from the pre-observation period. Open circle, placebo group; open triangle, nalfurafine 2.5-μg group; filled square, nalfurafine 5-μg group. All symbols show the mean value of VAS changes. *$P < 0.025$ vs. the placebo group, one-sided ANCOVA.

On day 7 of the treatment period, VAS changes in the 5-μg group ($P < 0.0001$) and the 2.5-μg group ($P = 0.0101$) were significantly larger than VAS change in the placebo group (*t* test, one-sided 2.5% significant level). The VAS changes in two nalfurafine groups were greater during the latter 7 days of the treatment period than those during the first 7 days of the treatment period.

During the post-observation period, the VAS changes were reduced compared with those during the latter 7 days of treatment period in two nalfurafine groups. The VAS changes were significantly smaller during the post-observation period (mean = 16 with 95% CI [13, 20]) than the VAS changes during the latter 7 days of the treatment period in the 5-μg group ($P < 0.0001$) and in the 2.5-μg group ($P < 0.0001$, paired *t* test, one-sided 2.5% significant level). In contrast, the VAS changes did not differ between the latter 7 days of the treatment period and the post-observation period (mean = 13 with 95% CI [10, 17]) in the placebo group ($P = 0.45$).

ADRs

The incidence of adverse events was 62.3% in the 5-μg group, 49.1% in the 2.5-μg group and 50.5% in the placebo group. The incidence of ADRs was 35.1% in the 5-μg group, 25.0% in the 2.5-μg group and 16.2% in the placebo group. The adverse events and ADRs with an incidence of ≥3% are shown in Table 3. Three patients each of the 5-μg and 2.5-μg nalfurafine groups discontinued the treatment because of ADRs, while no patient discontinued the treatment in the placebo group. Insomnia (sleep disturbance) led to the discontinuation of treatment in two patients each of the 5-μg and 2.5-μg nalfurafine groups.

Of the subjective symptoms and objective findings identified as ADRs, insomnia was reported the most frequently: 16 of the 114 patients in the 5-μg group and eight of the 112 patients in the 2.5-μg group complained of insomnia.

Moderate to severe ADRs were observed in five patients in each of 5-μg and 2.5-μg nalfurafine groups (10 cases in 5-μg group and six cases in 2.5-μg group). The moderate to severe ADRs reported in 5-μg group were anorexia (moderate in one patient), insomnia (moderate in two patients and severe in one patient), headache (moderate in one patient), pruritus (moderate in one patient), decreased blood thyroid stimulating hormone (TSH, moderate in one patient), mood altered (moderate in one patient), elevated mood (moderate in one patient) and feeling abnormal (moderate in one patient). The mood alterations in all the three patients were transient.

Moderate to severe ADRs reported in 2.5-μg group were insomnia (moderate in one patient), sudden hearing loss (moderate in one patient), hypertension (moderate in one patient), vomiting (moderate in one patient), nausea (moderate in one patient) and increased eosinophils (moderate in one patient). A moderate ADR (headache) was observed in one patient in the placebo group. All the other ADRs were mild.

The vital signs and electrocardiogram (ECG) findings exhibited no remarkable changes during the study. Regarding haematology and blood chemistry testing, none of the examined parameters exhibited remarkable changes during the study.

We monitored blood levels of prolactin and TSH as central hormones and free T_4 and free testosterone as peripheral ones. Transient increases in prolactin were found in three of 114 patients in the 5-μg group, three of 112 patients in the 2.5-μg group and one patient in the placebo group, while galactorrhoea was not reported. Decrease in TSH was found in two patients in the 5-μg group. Decrease in free testosterone was found in one patient each in the three groups. However, at the last observation, these changes returned to the levels of pre-observation period.

Table 3. Adverse events and ADR with an incidence of ≥3%

Item	5-μg group	2.5-μg group	Placebo group
Adverse events	Nasopharyngitis (12.3%) Insomnia (14.9%) Somnolence (3.5%) Constipation (7.9%)	Nasopharyngitis (8.0%) Insomnia (7.1%) Somnolence (4.5%) Diarrhoea (4.5%)	Nasopharyngitis (17.1%) Headache (3.6%) Vomiting (3.6%)
Adverse drug reactions	Insomnia (14.0%) Somnolence (3.5%) Constipation (7.0%)	Insomnia (7.1%) Somnolence (4.5%)	None

Discussion

Currently available antipruritic drugs, including antihistamines, antiallergics and topical corticosteroids, are sometimes effective for pruritus in dialysis patients but are not satisfactory [2–7]. The development of drugs effective for intractable pruritus is eagerly awaited not only in the field of chronic kidney disease and haemodialysis [3–5] but also in that of skin and liver diseases [11].

Nalfurafine hydrochloride (a novel κ-receptor agonist) has been shown to exhibit a prominent effect on intractable pruritus by a novel mechanism of action that differs from those of conventional drugs [14–18,20]. A series of data obtained in mice experiments explained the basic mechanisms underlying the suppressive effect of nalfurafine on itch and strongly support the data obtained in the present clinical study:

(1) Nalfurafine reduced the number of skin scratching episodes (index of itch) in mice with substance-P-induced itch (peripheral itching) and antihistamine-resistant itch without suppressing spontaneous locomotor activity [17].
(2) Nalfurafine also suppressed morphine-induced itching (mediated by the μ receptor in the CNS) in mice [21]. From these data, we speculate that the activation of the μ system in the CNS is implicated in the pathogenesis of itch and that the central κ system antagonizes the μ-receptor-mediated itch processing.
(3) A selective κ-receptor antagonist, norbinaltorphimine, induced itching in mice [22]. These findings together with the present clinical data imply that the κ system plays a role in the suppression of itch.

This randomized controlled Phase III study demonstrated the efficacy of nalfurafine hydrochloride administered at an oral dose of 5 μg per day and simultaneously examined the dose response of nalfurafine by comparison with a dose of 2.5 μg per day. The primary endpoint, decrease in the VAS value, was significantly larger in the 5-μg group than that in the placebo group. The efficacy of 5 μg of nalfurafine for the treatment of refractory pruritus in dialysis patients was thus demonstrated. In the 2.5-μg group, the VAS value also decreased and was significantly larger than in the placebo group.

Wikström *et al.* [18] gave 5 μg of nalfurafine or placebo intravenously in 144 patients after routine haemodialysis three times a week. Combining two prospective randomized studies, they demonstrated that intravenous nalfurafine significantly reduced the itch intensity and worst itching compared with placebo. In a first study of the report of Wikström *et al.* [18], the incidence of ADR was similar between 5 μg of intravenous nalfurafine (65%) and placebo (52%). The most common ADRs associated with nalfurafine were headache, nausea, insomnia and vertigo. In a second study, the incidence of ADR was also similar between 5 μg of nalfurafine (13%) and placebo (11%). The most common ADRs were vertigo and liver dysfunction.

The opioid μ system in the CNS has been considered as a cause of severe itch in uraemic patients [1,3,4] as well as mice [23]. Bigliardi *et al.* [24,25] found the μ receptors on keratinocytes of healthy humans and on the afferent sensory fibres running from epidermis to the CNS in patients with itch. These findings indicate the μ receptors in human skin to be implicated in itch. Recently, Takamori *et al.* [26] demonstrated κ receptors and its ligand dynorphin-A in human epidermis and keratinocytes by skin biopsy. The expression of the κ receptors was downregulated in patients with atopic dermatitis and itch, and the suppressed κ receptors were restored with psoralen-ultraviolet A therapy [26]. Considering these human data, we speculate that in the present study, nalfurafine acted on the κ receptors in the skin as well as in the CNS.

The most frequent ADR in this study was insomnia. Because insomnia was responsible for the discontinuation of treatment in four out of six patients, we should pay particular attention to this ADR. However, since all the ADRs were transient and readily resolved, nalfurafine may be considered a safe agent. In the present study, transient increases in prolactin were found in three of 114 patients in the 5-μg group, three of 112 patients in the 2.5-μg group and one patient in the placebo group, although galactorrhoea was not reported. In our 1-year open-label study giving 5 μg of nalfurafine in 211 haemodialysis patients with itch, we found transient increase of prolactin concentration in seven patients, decrease in TSH in four patients and decrease in free testosterone in two patients (H. Kumagai, unpublished data, 2009). We should closely observe the changes in these hormones. In the 1-year study, insomnia was also transient and short lived.

In summary, this prospective randomized, placebo-controlled study demonstrated that nalfurafine hydrochloride administered orally at doses of 5 μg and 2.5 μg was effective for reducing pruritus resistant to currently available treatments in haemodialysis patients and suggested that it poses minimal clinical safety problems.

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Conflict of interest statement. Hiroo Kumagai, Hidetomo Nakamoto, Taro Muramatsu and Hiromichi Suzuki occasionally worked as medical consultants in the development of anti-itch agents at Toray Industries, Inc. Toshiya Ebata and Kenji Takamori occasionally worked as medical consultants in the field of dermatology at Toray Industries, Inc.

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Continuous venovenous haemodialysis (CVVHD) and continuous peritoneal dialysis (CPD) in the acute management of 21 children with inborn errors of metabolism

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Abstract

Background. Newborns with inborn errors of metabolism often present with hyperammonaemic coma, requiring prompt diagnosis and specific medical therapy, nutritional support and efficient toxin removal. Little information regarding the efficacy and safety of continuous venovenous haemodialysis (CVVHD) as an option for extracorporal ammonia detoxification in children is available.

Methods. Twenty-one patients with hyperammonaemia [19 neonates (mean age 4.1±2.4 days) and two children 1 and 7