We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 3

Treatment Option for Uremic Pruritus

Hiromichi Suzuki, Hiroshi Omata and Hiroo Kumagai

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/59493

1. Introduction

Uremic pruritus remains a frequent concern for hemodialysis [HD] patients with the most frustrating and disabling symptoms. Nearly 90% of patients on dialysis suffer from pruritus. Until present, there have been a lot of reviews discussing the pathophysiology and treatment of pruritus[1-14]. Previously, the word "uremic pruritus" has been used for symptoms of itching because it is a common skin derangement in patients with advanced renal failure. However, the usage of "uremic" may cause confusion because pruritus is not found in patients with acute kidney injury. In this regard Paitel et al. [9] recently proposed the term, "chronic kidney disease (CKD)-associated pruritus" instead of "uremic pruritus" as a more precise nomenclature. In this review, the words "uremic pruritus", "CKD-associated pruritus" and "pruritus" are used interchangeably because the authors would like to respect each author's contribution. The prevalence of CKD-associated pruritus was found to range from 15-90% of patients [15, 16]. Recent data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that the prevalence of CKD-associated pruritus was 42% [17].

2. Clinical characteristics of CKD-associated pruritus

In patients with CKD, skin lesions are usually not found. Generally, skin lesions are secondary changes such as excoriations with or without impetigo, linear crusts, papules, and ulcerations. Half of patients have generalized itching, and in the other half, pruritus is localized to the back, limbs, chest or head. Pruritus is intermittent or prolonged over hours and days, and becomes worse at night [18, 19]. Mettang & Krener [14] stated in their review that the diagnosis of uremic

INTECH
open science | open minds

© 2015 The Author(s). Licensee InTech. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and eproduction in any medium, provided the original work is properly cited.

pruritus may be challenging because many patients with end-stage renal disease (ESRD) are suffering from other diseases, such as cardiovascular diseases, diabetes mellitus, chronic liver or hematological diseases, which may provoke itching either by itself or by medication given to treat these entities.

3. Why is pruritus problematic?

A recent longitudinal study of CKD-associated pruritus in HD patients have clearly demonstrated that significant associations were found among itching intensity, severity, and health-related quality of life [HR-QOL] measures in domains such as mood, social relations, and sleep. In Japan, Narita et al. [16] recruited a total of 1773 patients on HD and evaluated the severity of pruritus with a visual analogue scale (VAS). Four hundred and fifty-three patients had severe pruritus with a VAS score of more than or equal to 7.0. Further, 70% of these patients complained of sleep disturbances. From these data, it is clear that patients who suffer from pruritus also have a lower HR-QOL including sleep disturbances which may lead to poor prognosis.

4. Treatment for CKD-associated pruritus

4.1. Modification of dialysis techniques

The use of biocompatible dialysis membranes has been reported to reduce the prevalence of pruritus in HD patients [7]. However, it still remains uncertain whether alterations in dialysis therapy including changes in dialysis membrane can reduce pruritus [20, 21] or not [22]. Hiroshige et al. [23] analyzed data on 59 HD patients, who did not have disorders in calcium and phosphate metabolism, and found that more than 60% of them suffered from disabling pruritus possibly related to chronic uremia. Blood urea nitrogen [BUN] and plasma β_2-microglobulin, both of which are biochemical factors that are associated with the prevalence of pruritus and dialysis efficacy, were investigated and calculated by urea kinetics. After 3 months without changing the dialysis prescriptions, 16 patients had significant reductions of the pruritic score ranging from 12.6 ±5.1 to 6.3 ±3.2 ($P < 0.001$). From this study, the authors concluded that higher dialysis efficacy with good nutritional state reduces the prevalence and degree of pruritus in HD patients.

Previously, Graf et al. [24] reported that lowering the dialysate magnesium concentration can restore nerve conduction velocity towards normal in patients receiving HD, and this could be the reason for the complete disappearance of pruritus in the study by Hiroshige et al [25]. In contrast, Carmichael et al. [25] failed to demonstrate a beneficial effect of reduction in magnesium on pruritus. In their trial, although they showed that a magnesium-free dialysis fluid corrected hypermagnesaemia, it failed to improve renal itch. In addition, the fall in serum magnesium concentration was associated with an increased concentration of parathyroid hormone, as previously noted, with the potential of producing renal osteodystrophy in the

long term. It is therefore difficult to generalize the findings from the study by Hiroshige and colleagues.

The role of calcium in the dialysate was discussed by Kyriazi et al. [26], who showed that reduction in dialysis calcium concentrations from 1.75 to 1.0 mmol/L was associated with a 41.421 ± 8.47% ($P < 0.05$) relief from itching in 4 HD patients, indicating that at least in some uremic individuals, ionized calcium (iCa) has a pivotal role in the neuropathophysiology of CKD-associated pruritus. It has been postulated that calcium contributes to itching by influencing the degranulation of cutaneous mast cells, thus appearing to be a modifier rather than an initiator of CKD-associated pruritus.

Polymethylmethacrylate (PMMA) artificial kidney (AK) has been reported to adsorb more serum cytokines than other high-flux AK. In 30 patients with severe uremic pruritus out of 300 chronic patients in a single center who entered this prospective study, the dialyzers were changed to PMMA AK for 4 weeks. There were no significant differences in the laboratory assay results including predialysis serum BUN, creatinine (Cr), $\beta_2$microglobulin, calcium, phosphate, calcium-phosphate product, intact parathyroid hormone (iPTH), ferritin, hematocrit, high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-1β, IL-2, IL-6, IL-18, tumor necrosis factor (TNF)-α, and Kt/V. PMMA AK was effective in reducing the pruritus score from 23.46 ± 11.94 to 7.38 ± 6.42 ($P < 0.001$). The effect of uremic pruritus relief appeared after 1 week of PMMA AK use. In spite of this study, the mechanism for the beneficial effect of PMMA AK on uremic pruritus remains to be determined. However, it is proposed that PMMA AK may be a useful adjuvant therapy in chronic HD patients with severe uremic pruritus.

In line with this study, Kato et al. [27] carried out a prospective and crossover trial to investigate the effect of PMMA membrane on pruritus of HD patients with measurements of circulating levels of TNF-α and soluble TNF receptors (sTNFR-I, sTNFR-II) in 19 HD patients, who were complicated with prolonged severe pruritus for 6 months. However, there was no association between the degree of pruritus and circulating sTNFR-I and II values, although skin itching scale was significantly decreased following the use of PMMA membrane for 3 months. Combining with these finding together, it could be proposed that the PMMA dialyzer can improve renal itching.

4.2. Topical treatments

Emollients have been shown to be beneficial in patients with CKD-associated pruritus [28, 29, 30]. In general, emollients are proposed for use as first-line treatment. Among emollients, aqueous gels have been shown to reduce pruritus; previously, Okada and Matsumoto [31] demonstrated that emollients with high water content effectively reduced itch. In their report, 20 HD patients were divided into two groups; one group was treated with an aqueous gel containing 80% water (ADJUPEX Ensemble gel, ADJUPEX Co. Ltd. Tokyo, Japan) and another group did not receive any emollient treatment. The aqueous gel used in their study was composed by 80 g of water and 20 g of aloe vera extract, silk powder, naturally-derived vitamin E, squalane, and other naturally-derived ingredients. Moreover, the gel contained no synthetic and artificial substances. The emollient was applied twice daily for 2 weeks. VAS scores for itching at 2 weeks were significantly decreased compared with that at week 0. The results

showed that an aqueous gel containing high water content effectively improves itching in HD patients with mild uremic pruritus. Besides, psychological discomfort also improved.

The effects of aromatherapy on mood and anxiety in HD patients had been reported by Itai et al. [32] that in HD patients, hiba oil is an effective, non-invasive treatment for depression and anxiety.

A cream with structured physiological lipids (DMS, Derma Membrane Structure) and endogenous cannabinoids was tested for 3 weeks in 21 subjects with pruritus [30]. A significant reduction in pruritus was noted during the test product application using both scales for itching intensity assessment ($P < 0.0001$). Pruritus was significantly decreased at the end of the 3-week treatment ($P = 0.02$) as compared to before treatment, and was completely eliminated in eight patients (38.1%). This is the first study to evaluate topical application of a preparation containing endocannabinoids in the treatment of uremic pruritus. Dvorak et al.[33] showed that treatment with cannabionoid receptor agonists produced reduction of histamine-induced itching and had vasodilation by these topical application.

Another naturally-derived agent that may be helpful in reducing pruritus is capsaicin, which is an alkaloid extracted from the common pepper plant and marketed as a topical analgesic. Capsaicin has a potential antipruritic property with desensitization of nociceptive nerve endings depletion of substance P and then might block the conductor of pruritus. Breneman et al. [34] carried out an open-label, uncontrolled trial and a double-blind, vehicle-controlled trial to evaluate the efficacy and safety of capsaicin 0.025% cream in the treatment of localized areas of pruritus in patients undergoing long term HD. They found marked relief of itching without serious treatment-related adverse reactions.

Further, Tarng et al. [35] reported that 19 HD patients with idiopathic, moderate (n = 5) to severe (n = 14) pruritus were examined in a double-blind, placebo-controlled, crossover study. The results showed that capsaicin was significantly more effective than placebo and a prolonged antipruritic effect was observed 8 weeks post-treatment. Moreover, no serious side effects were noted during the study and there were no significant changes in serum concentrations of albumin, calcium, phosphorus, alkaline phosphatase, or iPTH during the treatment with either capsaicin or placebo. According to their results, this study provides indirect evidence that in idiopathic pruritus in some patients on maintenance HD, substance P may be transmitted from the peripheral sensory neurons to the central nervous system because local application of capsaicin depletes the peripheral neurons of substance P and may block the conduction of pruritus. In another study, Weisshaar et al. [36] reported that 11 pruritic patients on HD and 10 controls were treated with capsaicin 0.05% liniment on the upper back three times daily for 5 days. They reported that topical capsaicin showed some antipruritic potency in HD patients, providing that topical capsaicin might be one of the choice for treatment for HD patients with pruritus.

In addition to the components described above, essential fatty acids and their derivatives are necessary for normal cutaneous function and are thus proposed as potential treatments of pruritus. Tamimi et al. [37] found that primrose oil rich in the essential fatty acid gamma-linolenic acid (GLA) may be beneficial in alleviating pruritus. Chen et al. [38] found that GLA-

rich cream was better than placebo-based cream for alleviating uremic pruritus, thus it is a useful adjuvant in the management of refractory uremic pruritus.

A new topically active antipruritic medication has been derived from the Amazonian medicine Sangre de Grado [39]. The reported antipruritic effect on itch induced by insect bite was convincing, based on its role as a potent inhibitor of sensory afferent nerves. Moreover, Sangre de Grado is an effective analgesic and anti-inflammatory agent when applied topically.

Further, naturally-derived agents, chemical formulations, such as Tacrolimus, have also been studied, however there have been no convincing data reported until the present time [40, 41]. Topical steroids were also prescribed to these patients, probably based on the assumption that drugs used for itch in other conditions may also work on uremic pruritus, however, the absence of controlled studies and potential serious side effects of these agents dampen the routine prescription of such drugs to HD patients.

4.3. Ultraviolet irradiation

Ultraviolet, especially narrowband UVB, has been proposed as a potential therapeutic agent for pruritus. Although exact mechanisms of UVB therapy in CKD-associated pruritus is unknown, some possible explanations have been proposed such as inactivation of circulating pruritogenic substances [42, 43], suppression of histamine release from cutaneous mast cells [44], and reduction of cutaneous nerve fibers [45, 46]. Blachley et al. [47] reported that 17 patients presenting with severe pruritus were treated thrice weekly with total body exposure to either UVA or UVB light. UVB light resulted in resolution of pruritus in all cases. The mechanism by which UVB improves pruritus is not clear, but it has been suggested that it may in part be due to its ability to reduce cytokine production by lymphocytes.

4.4. Acupuncture

Acupuncture can be defined as the stimulation of anatomical points on the body using a variety of techniques for therapeutic purposes.

Recently, Kim et al. [48] reported a systemic review of acupuncture for treating uremic pruritus in patients with ESRD. According to their analysis, all of the included subjects reported beneficial effects of acupuncture. Che-yi et al. [49] randomized 40 HD patients with uremic pruritus into two groups and reported that; in group 1 (n = 20), acupuncture was applied unilaterally at the Quchi (LI11) acupoint thrice weekly for 1 month, and in group 2 (controls, n = 20), acupuncture was applied at a non-acupoint 2 cm lateral to Quchi (LI11) thrice weekly for 1 month. In their findings, pruritus scores before and after acupuncture, and at the 3-month follow-up were 38.3±4.3, 17.3± 5.5, and 16.5± 4.9 in group 1, and 38.3± 4.3, 37.5± 3.2, and 37.1± 5 in group 2 (controls), respectively. From these findings, the authors concluded that acupuncture at the Quchi (LI11) acupoint is an easy, safe, and effective method of relieving uremic pruritus.

In another study by Gao et al. [50], 68 cases were randomly divided by half into two groups, acupuncture or drug administration with chlor-trimenton and topical ointment for 2 weeks.

While receiving HD treatment, the acupuncture group received treatment at Quchi (LI11) with lifting-thrusting reducing method, and Zusanli (ST36) with lifting-thrusting reinforcing method for 30 min. In patients who received acupuncture therapy, after one course of treatment, 24 of 34 cases (70.6%) had complete alleviation of pruritus, 9 cases (26.5%) had obvious alleviation of pruritus, and 1 case had no improvement.

Sakurada et al. [51] reported that almost one-third of HD patients had undergone acupuncture or had a desire to try acupuncture treatment to manage common complications. Similar findings were also reported by Shapiro et al. [52] in an observational study. Further, electroacupuncture was performed on 7 HD patients with pruritus. Surprisingly, complete relief after one session of acupuncture treatment was reported in 6 patients and effects lasted up to one year.

Our group recently demonstrated a marked improvement of symptoms related with pruritus. Acupuncture was administered in 12 HD patients 1 to 3 times a week for one year. With improvement of these symptoms, QOL as evaluated by short form 36 (SF-36) health survey showed a marked increase in physical activity and sleep quality (personal communication). Interestingly, the BUN levels were significantly decreased, and those of hemoglobin increased although it did not reach statistical significance (Figs. 1-3).

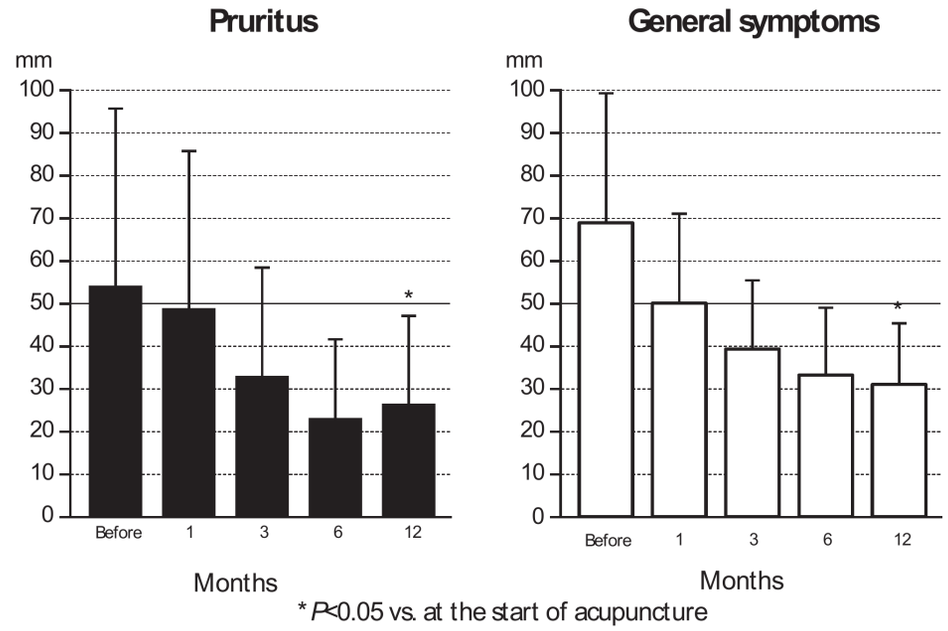


Figure 1. Changes in pruritus and general symptoms related with hemodialysis therapy by acupuncture 1 to 3 times a week for one year. Acupuncutre 1 to 3 times a week for one year produced a marked improvement in pruritus and general symptoms in patients with hemodialysis. * indicates P<0.05.

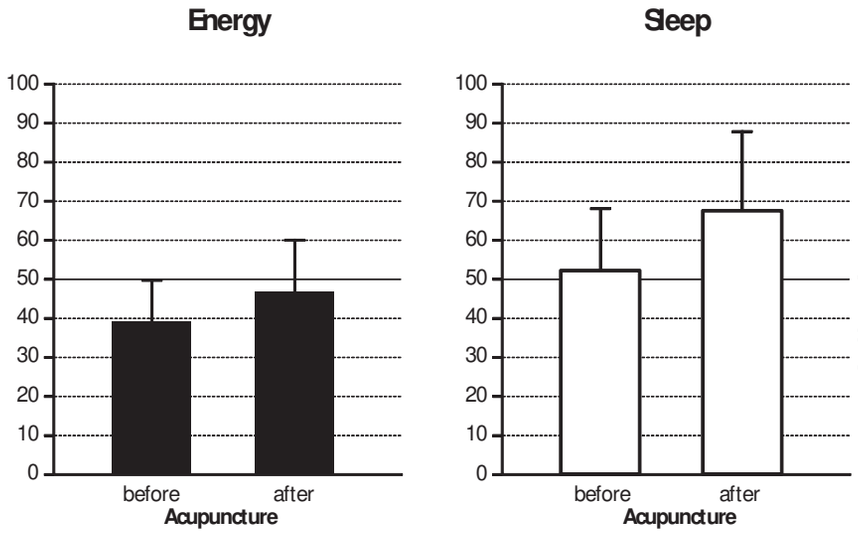


Figure 2. Changes in energy level and sleep of patients with hemodialysis by acupuncture 1 to 3 times a week for one year as evaluated by SF-36. Acupuncutre 1 to 3 times a week for one year produced a marked improvement in energy level and sleep in patients with hemodialysis.

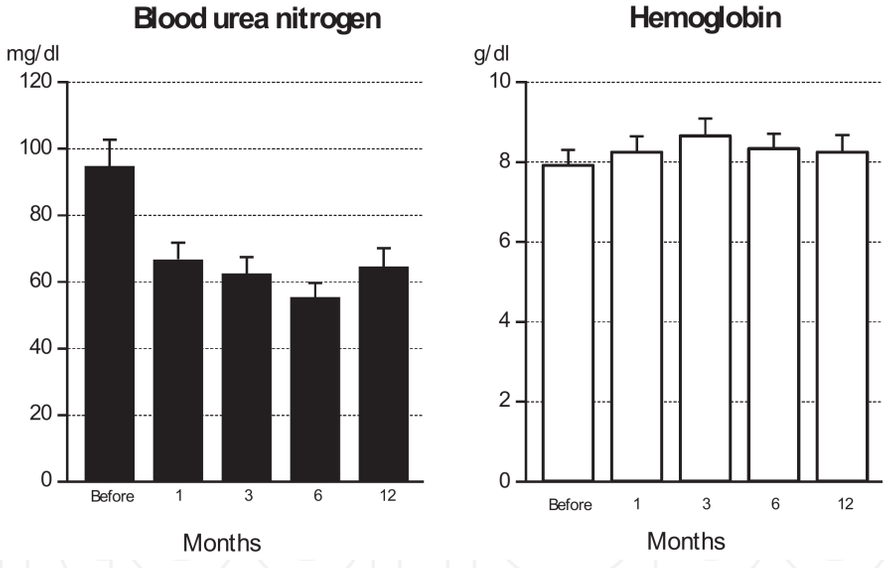


Figure 3. Changes in blood urea nitrogen and hemoglobin levels by acupuncture 1 to 3 times a week for one year. Acupuncutre 1 to 3 times a week for one year produced a marked improvement in blood urea nitrogen and hemoglobin levels in patients with hemodialysis.

4.5. Rubdown with Japanese dry towels

Our group examined the effects of "rubdown with Japanese dry towels" on CKD-associated pruritus. This method is a traditional Japanese alternative medical treatment to strengthen the barrier function of the skin. Briefly, subjects were naked or wore minimal clothing to maximally expose the skin of their body. Then, the subjects prepared three sets of Japanese dry towels

made with cotton. These towels were cleansed with water and then dried under sunlight. After drying, the subjects gently rubbed their whole body with these towels, and if possible, this procedure was carried out in direct sunlight. The results are shown in Fig.4. The mechanism by which this traditional Japanese alternative medical procedure aids in symptom relief may be because skin-rubbing produces secretion of corticosteroid hormone through stimulation of the thalamus [53]. Further, skin-rubbing eliminates the bacterial flora on the surface of the skin [54]. In combination with ultraviolet rays, skin-rubbing may prevent intrusion of c-fiber from the dermis into the epidermis which is one of the causes of itch [55, 56]

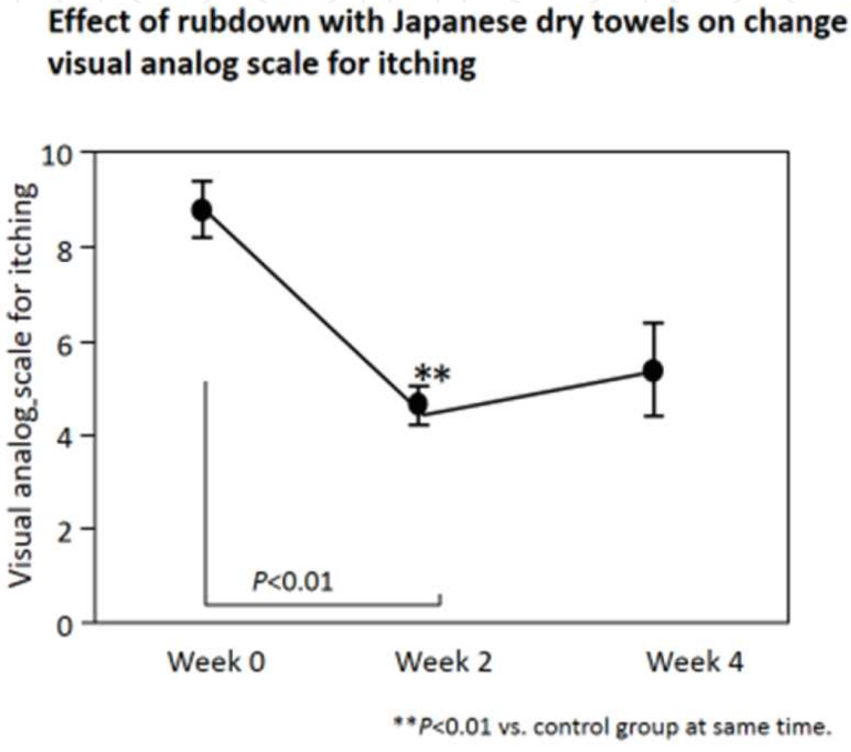


Figure 4. Effect of rubdown with Japanese dry towels on change in visual analog scale for itching. Manipulation by rubdown with Japanese dry towels produced a marked reduction in pruritus using the visual analog scale. ** indicates P<0.01.

4.6. Opioid antagonists

The use of opioid antagonists in uremic pruritus was first brought to our attention by Andersen et al. [57] when they published a case report about a terminally ill uremic patient successfully treated by naloxone for persistent itching. However, few studies were published, and these had conflicting findings. While Peer et al. [58] showed in a small placebo-controlled clinical trial that naltrexone, which is a μ-receptor antagonist, is effective, Pauli-Magnus et al. [40] failed to demonstrate any efficacy of naltrexone in the treatment of uremic pruritus. Later, Legroux-Crespel et al. [59] conducted a comparative study between naltrexone and loratadine, and concluded that naltrexone is not effective and not well-tolerated because of frequent side effects, except in a small subset of patients. More recently, another perspective was elaborated

regarding the use of a κ-agonist, for κ -receptor stimulation inhibits μ-receptor effects both peripherally and centrally, and hence might inhibit itching induced by substance P. In line with this concept, Wikstrom et al. [60] conducted two multicenter, randomized, double-blind, placebo-controlled studies that enrolled 144 patients with uremic pruritus to receive post-dialysis intravenous treatment with either nalfurafine, a novel κ -receptor agonist, or placebo for 2 to 4 weeks. Statistically significant reductions in itching, itching intensity, excoriations, and sleep disturbances were noted in the nalfurafine group as compared to the placebo group.

In light of all these findings, Toray Industries, Inc., Japan, recently developed nalfurafine, with refined opioid receptor affinity and selectivity, as an agent for relief of pruritus [61, 62]. In studies using animal models, nalfurafine exerted antipruritic activity not only for antihistamine-sensitive itch, but also for antihistamine-resistant itch [63, 64].

Kumagai et al. [65] carried out a prospective, randomized, double-blind comparative study for 2 weeks to compare the antipruritic effect of oral nalfurafine (2.5 and 5.0 μg) with a placebo in 337 patients. The mean pruritus value as assessed by VAS was 75.2 mm during the pre-observation period, which decreased significantly to 50.9 in weeks 2. The mean decrease in VAS from baseline was significantly larger in the 2 μg (n=112, P = 0.0001) and 5 μg (n=114, P = 0.0002) nalfurafine groups than in the placebo group (n=111). However, adverse drug reactions (ADRs) occurred in 103 patients, and the incidence was 25.0% in the 2.5 μg group, 35.1% in the 5 μg group, and 16.2% in the placebo group. The most common ADR was insomnia, observed in 24 of the 226 nalfurafine patients (22.3%). It is interesting to note that the group that received placebo also had a similar decrease in itching. It is well known that placebo-induced expectancies have been shown to decrease pain in a manner reversible by opioid antagonists. This phenomenon is corroborated by the findings of Wager et al. [66], who demonstrated using functional magnetic resonance image that placebo analgesia was related to decreased brain activity in pain-sensitive brain regions, including the thalamus, insula, and anterior cingulate cortex.

Further, Kumagai et al. [67] carried out an open-label study examining the effects and ADRs of 52-week oral administration of nalfurafine hydrochloride in 211 HD patients with treatment-resistant itch. They found that the mean pruritus values as assessed by the VAS was 75.2 mm during the pre-observation period, which decreased significantly to 50.9 and 30.9 mm in weeks 52, indicating a long-lasting efficacy. ADRs occurred in 103 patients. Frequent ADRs were insomnia (19.4%), constipation (7.1%), and increased blood prolactin (3.3%).

5. Future perspectives

As stated in this review, recent advances in pathophysiology of itch and treatment for CKD-associated pruritus have improved this condition remarkably, however, there are still a lot of obstacles to overcome in order to achieve satisfactory comfort and relief from unpleasant symptoms stemming from pruritus. It is therefore of the utmost importance for investigators and physicians to study and research in this area.

Author details

Hiromichi Suzuki[1*], Hiroshi Omata [2] and Hiroo Kumagai[3]

*Address all correspondence to: iromichi@saitama-med.ac.jp

1 Department of Nephrology, Saitama Medical University, Japan

2 Department of Oriental Medicine, Saitama Medical University, Japan

3 Department of Nephrology and Endocrinology National Defense Medical College, Japan

References

[1] Stahle-Backdahl M. Uremic pruritus. Clinical and experimental studies. Acta Derm Venereol Suppl [Stockh]. 1989;145:1-38.

[2] Stahle-Backdahl M. Pruritus in hemodialysis patients. Skin Pharmacol. 1992;5:14-20.

[3] Stahle-Backdahl M. Uremic pruritus. Semin Dermatol. 1995;14:297-301.

[4] Manenti L, Tansinda P, Vaglio A. Uraemic pruritus: clinical characteristics, pathophysiology and treatment. Drugs. 2009;69:251-63.

[5] Yosipovitch G, Greaves MW, Schmelz M. Itch. The Lancet. 2003;361:690-4.

[6] Lugon JR. Uremic pruritus: a review. Hemodial Int. 2005;9:180-8.

[7] Kosmadakis GC, Zerefos N. Uremic pruritus. Int J Artif Organs. 2006;29:938-43.

[8] Greaves MW. Recent advances in pathophysiology and current management of itch. Ann Acad Med Singapore. 2007;36:788-92.

[9] Patel TS, Freedman BI, Yosipovitch G. An update on pruritus associated with CKD. Am J Kidney Dis. 2007;50:11-20.

[10] Narita I, Iguchi S, Omori K, Gejyo F. Uremic pruritus in chronic hemodialysis patients. J Nephrol. 2008;21:161-5.

[11] Berger TG, Steinhoff M. Pruritus and renal failure. Semin Cutan Med Surg. 2011;30:99-100.

[12] Greaves MW. Pathogenesis and treatment of pruritus. Curr Allergy Asthma Rep. 2010;10:236-42.

[13] Kfoury LW, Jurdi MA. Uremic pruritus. J Nephrol. 2012;25:644-52.

[14] Mettang T, Kremer AE. Uremic pruritus. Kidney Int. advance online publication, 8 January 2014;doi:10.1038

[15] Pontremoli R, Sofia A, Ravera M, Nicolella C, Viazzi F, Tirotta A, et al. Prevalence and clinical correlates of microalbuminuria in essential hypertension The MAGIC Study. Hypertension. 1997;30:1135-43.

[16] Narita I, Alchi B, Omori K, Sato F, Ajiro J, Saga D, et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. Kidney Int. 2006;69:1626-32.

[17] Pisoni RL, Wikstrom B, Elder SJ, Akizawa T, Asano Y, Keen ML, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2006;21(12):3495-505.

[18] Gilchrest BA, Stern RS, Steinman TI, Brown RS, Arndt KA, Anderson WW. Clinical features of pruritus among patients undergoing maintenance hemodialysis. Arch Dermatol. 1982;118:154-6.

[19] Dar NR, Akhter A. Clinical characteristics of uremic pruritus in patients undergoing haemodialysis. J Coll Physicians Surg Pak. 2006;16:94-6.

[20] Liakopoulos V, Krishnan M, Stefanidis I, Savaj S, Ghareeb S, Musso C, et al. Improvement in uremic symptoms after increasing daily dialysate volume in patients on chronic peritoneal dialysis with declining renal function. Int Urol Nephrol. 2004;36:437-43.

[21] Szepietowski JC, Reich A, Szepietowski T. Emollients with endocannabinoids in the treatment of uremic pruritus: discussion of the therapeutic options. Ther Apher Dial. 2005;9:277-9.

[22] Novak MJ, Sheth H, Bender FH, Fried L, Piraino B. Improvement in Pittsburgh Symptom Score index after initiation of peritoneal dialysis. Adv Perit Dial. 2008;24:46-50.

[23] Hiroshige K, Kabashima N, Takasugi M, Kuroiwa A. Optimal dialysis improves uremic pruritus. Am J Kidney Dis. 1995;25:413-9.

[24] Graf H, Kovarik J, Stummvoll HK, Wolf A. Disappearance of uraemic pruritus after lowering dialysate magnesium concentration. Br Med J. 1979;2(6203):1478-9.

[25] Carmichael AJ, Dickinson F, McHugh MI, Martin AM, Farrow M. Magnesium free dialysis for uraemic pruritus. BMJ. 1988;297(6663):1584-5.

[26] Kyriazis J, Glotsos J. Dialysate calcium concentration of</=1.25 mmol/l: is it effective in suppressing uremic pruritus? Nephron. 2000;84:85-6.

[27] Kato A, Takita T, Furuhashi M, Takahashi T, Watanabe T, Maruyama Y, et al. Polymethylmethacrylate efficacy in reduction of renal itching in hemodialysis patients: crossover study and role of tumor necrosis factor-alpha. Artif Organs. 2001;25:441-7.

[28] Morton CA, Lafferty M, Hau C, Henderson I, Jones M, Lowe JG. Pruritus and skin hydration during dialysis. Nephrol Dial Transplant. 1996;11:2031-6.

[29] Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, et al. Itch: scratching more than the surface. QJM. 2003;96:7-26.

[30] Szepietowski JC, Szepietowski T, Reich A. Efficacy and tolerance of the cream containing structured physiological lipids with endocannabinoids in the treatment of uremic pruritus: a preliminary study. Acta Dermatovenerol Croat. 2005;13:97-103.

[31] Okada K, Matsumoto K. Effect of skin care with an emollient containing a high water content on mild uremic pruritus. Ther Apher Dial. 2004;8:419-22.

[32] Itai T, Amayasu H, Kuribayashi M, Kawamura N, Okada M, Momose A, et al. Psychological effects of aromatherapy on chronic hemodialysis patients. Psychiatry Clin Neurosci. 2000;54:393-7.

[33] Dvorak M, Watkinson A, McGlone F, Rukwied R. Histamine induced responses are attenuated by a cannabinoid receptor agonist in human skin. Inflamm Res. 2003;52:238-45.

[34] Breneman DL, Cardone JS, Blumsack RF, Lather RM, Searle EA, Pollack VE. Topical capsaicin for treatment of hemodialysis-related pruritus. J Am Acad Dermatol. 1992;26:91-4.

[35] Tarng DC, Cho YL, Liu HN, Huang TP. Hemodialysis-related pruritus: a double-blind, placebo-controlled, crossover study of capsaicin 0.025% cream. Nephron. 1996;72:617-22.

[36] Weisshaar E, Dunker N, Gollnick H. Topical capsaicin therapy in humans with hemodialysis-related pruritus. Neurosci Lett. 2003;345:192-4.

[37] Tamimi NA, Mikhail AI, Stevens PE. Role of gamma-linolenic acid in uraemic pruritus. Nephron. 1999;83:170-1.

[38] Chen YC, Chiu WT, Wu MS. Therapeutic effect of topical gamma-linolenic acid on refractory uremic pruritus. Am J Kidney Dis. 2006;48:69-76.

[39] Miller MJS, Vergnolle N, McKnight W, Musah RA, Davison CA, Trentacosti AM, et al. Inhibition of Neurogenic Inflammation by the Amazonian Herbal Medicine Sangre de Grado. 2001;117:725-30.

[40] Pauli-Magnus C, Mikus G, Alscher DM, Kirschner T, Nagel W, Gugeler N, et al. Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. J Am Soc Nephrol. 2000;11:514-9.

[41] Duque MI, Thevarajah S, Chan YH, Tuttle AB, Freedman BI, Yosipovitch G. Uremic pruritus is associated with higher kt/V and serum calcium concentration. Clin Nephrol. 2006;66:184-91.

[42] Gilchrest BA, Rowe JW, Brown RS, Steinman TI, Arndt KA. Ultraviolet phototherapy of uremic pruritus. Long-term results and possible mechanism of action. Ann Intern Med. 1979;91:17-21.

[43] Shultz B, Roenigk H. Uremic pruritus treated with ultraviolet light. JAMA. 1980;243:1836-7.

[44] Imazu LE, Tachibana T, Danno K, Tanaka M, Imamura S. Histamine-releasing factor[s] in sera of uraemic pruritus patients in a possible mechanism of UVB therapy. Arch Dermatol Res. 1993;285:423-7.

[45] Fjellner B, Hagermark O. Influence of ultraviolet light on itch and flare reactions in human skin induced by histamine and the histamine liberator compound 48/80. Acta Derm Venereol. 1982;62:137-40.

[46] Wallengren J, Sundler F. Phototherapy reduces the number of epidermal and CGRP-positive dermal nerve fibres. Acta Derm Venereol. 2004;84:111-5.

[47] Blachley JD, Blankenship DM, Menter A, Parker TF, 3rd, Knochel JP. Uremic pruritus: skin divalent ion content and response to ultraviolet phototherapy. Am J Kidney Dis. 1985;5:237-41.

[48] Kim KH, Lee MS, Choi SM. Acupuncture for treating uremic pruritus in patients with end-stage renal disease: a systematic review. J Pain Symptom Manage. 2010;40:117-25.

[49] Che-Yi C, Wen CY, Min-Tsung K, Chiu-Ching H. Acupuncture in haemodialysis patients at the Quchi (LI11) acupoint for refractory uraemic pruritus. Nephrol Dial Transplant. 2005;20:1912-5.

[50] Gao H, Zhang W, Wang Y. Acupuncture treatment for 34 cases of uremic cutaneous pruritus. J Tradit Chin Med. 2002;22[1]:29-30.

[51] Sakuraba H, Takeuchi H, Takeuchi M, Syoji M, Moriyama T. Questionnaire survey of complaints and accupuncutre treatment in maintenance hemodialysis patients. Nihon Toseki Igakkai Zasshi 2007;40:513-6.

[52] Shapiro R, Stockard H, Schank A. Successful treatment of uremic pruritus with acupuncutre.. Am J Acupunct. 1986;14:235-42.

[53] Antoni F. Hypothalamic control of adrenocorticotropin secretion : advnaces ince the discovery of 41-redue corticotropin-releasing factor. Endocr Rev. 1986;7:351-78.

[54] Percival SL, Emanuel C, Cutting KF, Williams DW. Microbiology of the skin and the role of biofilms in infection. Int Wound J. 2012;9:14-32.

[55] Tominaga M, Takamori K. An update on peripheral mechanisms and treatments of itch. Biol Pharm Bull. 2013;36:1241-7.

[56] Tominaga M, Takamori K. Sensitization of Itch Signaling: Itch Sensitization-Nerve Growth Factor, Semaphorins. 2014.

[57] Andersen LW, Friedberg M, Lokkegaard N. Naloxone in the treatment of uremic pruritus: a case history. Clin Nephrol. 1984;21:355-6.

[58] Peer G, Kivity S, Agami O, Fireman E, Silverberg D, Blum M, et al. Randomised crossover trial of naltrexone in uraemic pruritus. Lancet. 1996;348:1552-4.

[59] Legroux-Crespel E, Cledes J, Misery L. A comparative study on the effects of naltrexone and loratadine on uremic pruritus. Dermatology. 2004;208:326-30.

[60] Wikstrom B, Gellert R, Ladefoged SD, Danda Y, Akai M, Ide K, et al. Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. J Am Soc Nephrol. 2005;16:3742-7.

[61] Seki T, Awamura S, Kimura C, Ide S, Sakano K, Minami M, et al. Pharmacological properties of TRK-820 on cloned mu-, delta- and kappa-opioid receptors and nociceptin receptor. Eur J Pharmacol. 1999;376:159-67.

[62] Nagase H, Hayakawa J, Kawamura K, Kawai K, Takezawa Y, Matsuura H, et al. Discovery of a structurally novel opioid kappa-agonist derived from 4,5-epoxymorphinan. Chem Pharm Bull (Tokyo). 1998;46:366-9.

[63] Wakasa Y, Fujiwara A, Umeuchi H, Endoh T, Okano K, Tanaka T, et al. Inhibitory effects of TRK-820 on systemic skin scratching induced by morphine in rhesus monkeys. Life Sci. 2004;75:2947-57.

[64] Togashi Y, Umeuchi H, Okano K, Ando N, Yoshizawa Y, Honda T, et al. Antipruritic activity of the kappa-opioid receptor agonist, TRK-820. Eur J Pharmacol. 2002;435:259-64.

[65] Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H, Suzuki H. 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. Nephrol Dial Transplant. 2010;25:1251-7.

[66] Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, et al. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science. 2004;303:1162-7.

[67] Kumagai H, Ebata T, Takamori K, Miyasato K, Muramatsu T, Nakamoto H, et al. Efficacy and safety of a novel k-agonist for managing intractable pruritus in dialysis patients. Am J Nephrol. 2012;36:175-83.