Chapter 2

Uremic Pruritus; Its Prevalence, Pathophysiology and Management

Pornanong Aramwit and Ouppatham Supasyndh

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1. Introduction

Pruritus is a nociceptive sensation transmitted centrally from the periphery by the unmyelinated, large, slowly conductive C fibers [1]. Pruritus is the dominant symptom of skin disease and a frequent manifestation of systemic disease. Of all of the systemic disorders, uremia is certainly the most important cause of pruritus [2]. The association between uremia and pruritus was first reported more than a century ago. Patients with severe chronic renal failure may be predisposed to the development of xerosis, hyperpigmentation, uremic roseola, calcinosis cutis, acquired perforating dermatosis, bullous dermatosis of hemodialysis, half and half nails and pruritus [3,4]. However, pruritus is often the most difficult to manage [5] and also related to mortality of end-stage renal disease (ESRD) patients. Aside from kidney transplantation, which is the only definitive treatment, therapeutic approaches for the treatment of pruritus have largely been empirical. The main goal of therapy remains to minimize the severity of pruritus and improve the quality of life, especially among those who are not transplantation candidates or are waiting for surgery.

Uremic pruritus (UP) may not be associated with the initiation of hemodialysis therapy, or symptoms may first become apparent with it [6]. A global study reported a 42% prevalence of moderate or extreme UP, which was strongly associated with sleep disturbance, depression, impaired quality of life and mortality [7]. Another study noted a higher percentage of pruritus in patients with more advanced chronic kidney disease (CKD): 18% of stage 3, 26% of stage 4, 42% of stage 5 and 58% of stage 5 CKD on maintenance hemodialysis for 1 month or greater [8] experienced UP. Once pruritus manifests itself, it often persists [6]. Pruritus can be a temporary condition lasting only a few months, but more commonly, it affects patients for more than 1 year. About one quarter of patients suffer from it only during or soon after hemodialysis, whereas others find this period a time of pruritus symptomatic exacerbation [9,10]. The intensity of pruritus was described as mild in 22- 52.6%, moderate in 22.6- 40% and

severe in 8- 40% of patients [10-12]. About half of UP patients suffer from continuous itch, while the others experience it only occasionally with episodes of exacerbation. UP affects quality of life because of serious discomfort, anxiety, depression and sleeping disorders, especially because it is usually worse at night [13]. Pruritus may increase in intensity during the summer months, possibly due to the rising skin temperature reducing the threshold for the perception of UP, as occurs in other types of pruritus [14]. For that reason, external heat, sweat and stress can aggravate UP, and cold or hot showers can alleviate the symptoms [15]. The skin may appear normal or display different types of lesions, mostly related to scratching (e.g., lichen simplex, prurigo nodularis or keratosis papules) [13].

UP may be localized or generalized. Generalized itching is evident in about half of the patients [6]. Pruritus in dialysis patients is most commonly localized to the back, followed by the forearm with an arterio-venous fistula (perhaps due to frequent washing and traumatization of this region), abdomen, or head [16]. It has been reported that patient age, sex, underlying renal disease or dialysate solution used for hemodialysis (bicarbonate-based or acetate-based) have no influence on UP [6,10]. However, using less permeable and less biocompatible dialysis membranes show higher incidence of pruritus [6,10]. Moreover, patients with longer period of hemodialysis (> 3 months) may have high tendency to experience UP [13], possibly due to the accumulation of undefined pruritogenic cytokines or other substances [10].

Different scoring systems were used to quantify the severity of UP in clinical trials. The most commonly used include the visual analogue score (VAS) [17-19], a 4-point pruritus score [20] and a comprehensive validated questionnaire that was developed based on a short form of the McGill pain questionnaire [17,21]. This questionnaire was found to be reliable and provided valid data on the sensory, affective and overall intensity of UP and may provide a basis for future cross-cultural studies of itching [17] and for other study-specific scales [22].

Clinical appearance of UP can be observed by secondary changes such as atrophy of adnexal structures, microangiopathy with necrosis of endothelial cells, changes of sebaceous glands, lesions or lichen complex chronicus, excoriations and prurigo nodularis [23]. Although hemodialysis and continuous ambulatory peritoneal dialysis (CAPD) seem to be associated with a similar incidence of UP [24,25], some have found its incidence with CAPD was 10% [4] to 14% [26] lower, possibly due to a more effective elimination of possible pruritogenic substances by the peritoneum than by artificial membranes [27].

Due to the effect of UP which can cause serious discomfort, severe anxiety or even depression and sleeping disorders, it really affect patients' quality of life. Since sleeping disorders are related to chronic fatigue, it has strong influence on mental and physical health of patients [15]. Recently, studies demonstrated an association between UP and an increased risk of mortality [7,19].

2. Pathophysiology

The pathophysiology for this condition is not well understood. Known risk factors that predispose patients to UP are male gender [19], although some studies showed a higher prevalence in females [22,28], high levels of blood urea nitrogen and elevated calcium, phosphorus and β_2-microglobulin [22,29]. Other contributing factors include hypervitaminosis

A [20], high aluminum levels [30], anemia, erythropoietin insufficiency, elevated ferritin, low transferrin, low albumin, peripheral neuropathy [31] and secondary hyperparathyroidism with elevated divalent ions such as calcium, phosphate and magnesium ions [22]. Xerosis, which is very frequent in uremic patients as a result of a decrease in sweat volume as well as atrophy of the sebaceous glands and dehydration of the stratum corneum, may indeed play a role in UP.

It is hypothesized that UP is caused by the metabolic disequilibrium of CKD [32]. Some studies mentioned that it involves cutaneous nerve proliferation, pruritogenic cytokines or other chemicals, mast cell proliferation and secondary hyperparathyroidism. [5] Others propose that a poorly dialyzable substance is responsible for UP due to its systemic accumulation but that this resolves with renal transplantation [32]. UP has also been proposed to be a manifestation of multisystem dysfunction that is comorbid with renal failure. Proinflammatory mediators such as T-helper (Th)-1 cytokine and interleukin (IL)-2 may play a role in pruritus. Hypercalcemia and hyperphosphatemia with secondary deposition of calcium phosphate crystals in the skin may also contribute to itch [32]. Some biochemical parameters have been reported to be associated with the development of UP including magnesium [33], intact-parathyroid hormone (iPTH) [34], phosphate [33] and calcium [35]. While uremia may cause pruritus, other etiologies of pruritus must also be ruled out. Patients must be evaluated for endocrine disorders, atopic dermatitis, infestations, psychiatric disorders (e.g., delusions parasitosis), contact dermatitis and allergic reactions to the dialysate [23].

In UP, the stimulation of free nerve endings or dermal itch receptors generate impulses via C-fibers to the spinal cord and further to thalamus and finally reach cerebrum [36]. It is believed that substance P, which is a type of neurotransmitter, is a key to transmit the sensation of itch [3].

The physical appearances of skin in patients with chronic renal failure are totally difference from healthy people. Microangiopathy, thickening of basement membrane, epidermal atrophy or atrophy of sebaceous glands are normally found in hemodialysis patient [37,38,39]. Due to the lower levels of fat and water content on stratum corneum of skin with chronic kidney diseases, pruritus is normally found [40]. Reduction of sweat is another factor related to UP since the amount of electrolytes, lactate, urea, protein, lipids and amino acid elimination are normally decreased [40]. There is a positive correlation between xerosis and pruritus [11,25], but no correlation between cutaneous water content or transepidermal water loss and pruritus has been found [41,42]. However, the stratum corneum layers on the skin of dialysis patients are significantly less hydration compared to healthy skin [43].

There are several reports indicated that serum levels of divalent ions such as magnesium, calcium, aluminum and phosphate are related to UP [3,10,40,44]. Magnesium can stimulate neuron or activate histamine releasing from mast cells [45] while calcium and phosphate can induce itch receptors and cause metastatic cutaneous calcification [10,30]. An elevated serum aluminum concentration in chronic hemodialysis patients with UP was also reported as a possible etiology [30].

Secondary hyperparathyroidism has been proposed as a possible cause of UP, and normally, end-stage renal disease (ESRD) patients develop secondary hyperparathyroidism [3,46]. However, UP is relieved after parathyroidectomy [46]. Although hyperparathyroidism in UP is frequently associated with pruritus [47], a positive correlation was not confirmed [3]. Intact

parathyroid hormone is not related to UP while mid-region parathyroid hormone (m-PTH) shows some correlation [6]. In patients with UP, the large amounts of inactive carboxy-terminal metabolites of parathyroid hormone is normally found in serum [6].

Mast cell accumulation and degranulation may play a role in UP [10,48,49]. Parathyroid hormone is known to stimulate mast cell production and accumulation in various organs [49]. Some studies have shown an increased number of cutaneous mast cells in uremic patients compared with healthy subjects [10,38], but very few reports show the correlation between mast cells and pruritus [47,50]. Very numerous, degranulated mast cells with diffusely distribution within dermis are normally found in patients with UP while mast cells in healthy subjects are mainly localized and intact in the upper dermis [10,51].

Mediators of inflammation may also be important. Histamine, a well-known mediator of pruritus in dermatologic disease, is elevated in the plasma of patients with ESRD as a result of histamine retention in renal insufficiency [52]. Histamine is released from mast cells in response to substance P and is thought to be implicated in UP. The number of mast cells is increased in patients with CKD, and increased plasma levels of tryptase and histamine have been reported in patients with severe UP [53]. In addition, prostaglandins are thought to modulate pruritus by lowering the threshold for histamine-induced pruritus [54]. There is a correlation between plasma histamine levels and pruritus [52,55]. It is found that histamine levels in patients with UP is significant higher compared to nonpruritic subjects [52,55] but specific differences in plasma histamine levels in subjects with and without UP cannot be found [26,56]. Since antihistamine has been widely used but ineffective for the treatment of UP, histamine should not have a significant role for this symptom [57].

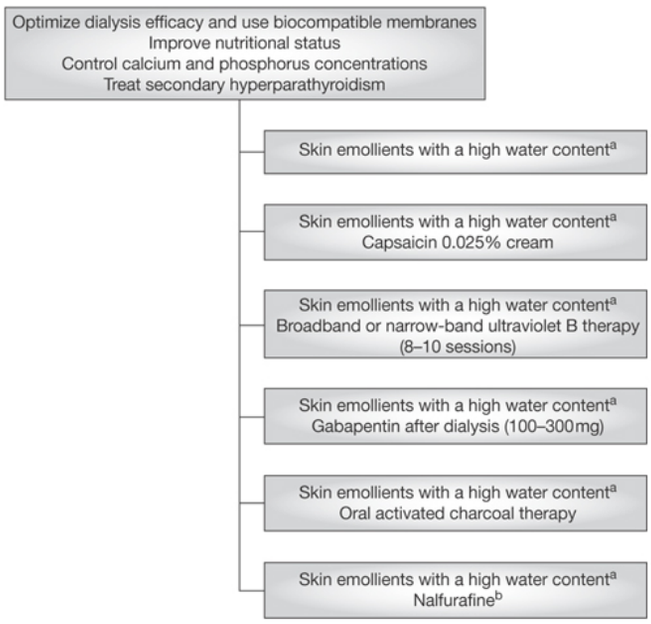
It is possible that there are unknown pruritogenic cytokines produced by activated cells in some itching dermatoses [36]. Nitric oxide was also postulated to have a possible role in the development of UP [58], as it can be synthesized from cells under inflammatory stimulants including tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and IL-1β, and it has cytotoxic effects that can be involved in inflammatory dermatoses. During hemodialysis, several cytokines, including IL-1, are released following contact between plasma and the dialysis membrane [59]. IL-1 has been postulated to induce the release of inflammatory and potentially pruritogenic substances [6].

The two newest hypotheses that were proposed to explain the underlying pathophysiological mechanisms of UP are the immune hypothesis and the opioid hypothesis [22]. The immune hypothesis considers UP to be an inflammatory systemic disease [21] with over-activation of $CD4^{+}TH1$ lymphocytes and overproduction of IL-2, IFN-γ and TNF-α. IL-2 is released during hemodialysis secondary to the contact of blood and dialysis membranes [60], and it is known to be pruritogenic when injected into the skin. The increased serum levels of inflammatory biomarkers such as C-reactive protein and IL-6 confirms the inflammatory nature of the disease [61]. For the opioid hypothesis, it is well known that opioids play a role in modulating the sensation of pruritus both centrally and peripherally. Endogenous opioids are known to play a role in cholestatic prutitus [22], but it was also postulated that they have a role in UP secondary to the overexpression of opioid μ-receptors in dermal cells and lymphocytes, and concomitant down-regulation of opioid κ-receptors caused by the increase in serum β-endorphin to endorphin A ratio that is observed in patients with CKD [62]. Despite all these mechanisms, the certain pathophysiology of UP remains unknown.

3. Treatment

Despite high prevalence and life-altering comorbidities, UP remains poorly characterized and lacks effective treatment [63]. Because the pathophysiological mechanisms of UP are poorly understood, the treatments have largely been empirical, and no treatment has been shown to have sufficient efficacy and safety [64]. Moreover, no drugs have been approved by the U.S. Food and Drug Administration for this problem. Before considering the treatment of UP, an evaluation should be performed to define whether pruritus in a specific patient is caused by uremia (which needs adequate dialysis) or is related to dermatologic or systemic disease such as hyperparathyroidism, hyperphosphatemia and anemia that may require a different approach [2]. Once the etiology of pruritus has been established, several therapies can potentially be adopted. Treatments can be classified as topical, physical or systemic applications.

In order to control UP in dialysis patients, several factors need to be monitored such as improvement of nutritional status, monitoring of calcium and phosphorus levels, optimization of dialysis efficacy as well as use of biocompatible dialysis membranes [65]. Pruritus found in CKD may cause from other disorders such as liver diseases (for instance; hepatitis), endocrine disorders (for instance; Graves' disease, diabetes mellitus and hypothyroidism) and skin disorders (such as atopic dermatitis, psoriasis, contact dermatitis and urticaria). Pruritus found in these causes need specific treatments which may differ from standard treatment [53]. A step-up therapeutic approach for UP in patients with CKD is presented in Figure 1.



[a] Use of evening primrose oil rich in essential fatty acids (γ-linolenic acid), bath oil that contains polidocanol and cream that contains natural lipids and endocannabinoids can be attempted if simple emollients fail.

[b] For intractable UP that does not respond to nalfurafine (5 μg intravenously thrice weekly for 4 weeks), treatment with short courses of topical tacrolimus ointment (0.1% for 2-6 weeks) or oral thalidomide (100 mg daily for 2-4 weeks) can be attempted.

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Figure 1. Step-up therapeutic approach for UP in a patients with CKD.

4. Physical Treatments

4.1. Modification of Dialysis Techniques and Mineral Abnormalities

The prevalence of UP declines by using biocompatible dialysis membranes [66]. Hence, the first approach to improve UP is still to optimize the dialysis efficiency, use biocompatible dialysis membranes and improve the nutrition status of patients. One study demonstrates that in a series of 30 cases, a polymethylmethacrylate (PMMA) artificial kidney may be a useful adjuvant therapy in chronic hemodialysis patients with severe UP, as it may eliminate more serum cytokines by adsorption than other types of high-flux membranes [67].

Because divalent ions, including magnesium and calcium, may possibly be involved in the pathogenesis of uremia, using a hemodialysis bath with low calcium and magnesium concentration [45,68,69] and keeping the calcium × phosphate product less than 55 mg^2/dL^2 can play a role in improving the pruritus [35]. However, drastic reduction in dialysate calcium concentration may possibly aggravate renal osteodystrophy.

4.2. Efficient Dialysis

It is a common experience that pruritus is more frequent in underdialyzed patients and improves by increasing the efficacy of dialysis. Pruritus patients tend to have higher blood urea nitrogen and lower K_t/V values [70]. Increasing the K_t/V from a mean of 1.05 to 1.24 in severely pruritic patients improved their symptoms significantly [70].

4.3. Parathyroidectomy

Patients who experience pruritus together with hypercalcemia and hyperparathyroidism should be treated by parathyroidectomy [46,71]. However, there is no relation between parathyroid hormone and UP, parathyroidectomy should not be used as a routine procedure [2]. It was found that patients with hypocalcemia or serum calcium at the normal limit can still experience pruritus. It can be concluded that the relationship between serum calcium level and pruritus is hardly found [72].

4.4. Phototherapy

The role of phototherapy in renal pruritus has been assessed by double-blind trials. Ultraviolet B (UVB) has been generally, although not uniformly, shown to be therapeutic. The mechanism of the antipruritic effect of UVB is not completely understood. Among the proposed mechanisms are inactivation of a circulating pruritogenic substance, formation of a photo-product that relieves pruritus, alteration of divalent ion content in the skin, suppression of histamine release as well as deactivation of circulating pruritogenic substances [16] and promotion of cutaneous nerve degeneration [73,74]. UVB phototherapy is well tolerated aside from occasional instances of sunburn [75]. The duration of the antipruritic effect of thrice-weekly, total body UVB phototherapy (8- 10 sessions in total) is variable but can last for several months. In

1975, Saltzer *et al*. first described successful treatment with irradiation of UVB (wavelength 280- 315 nm), [76] and the results were confirmed by several studies [32,75,77,78]. The study also showed that there was no significant difference between remission rates or length of remission between the intensive, intermediate and prolonged treatment schedule [75,79].

Later, a study by Blachley *et al*. not only showed the efficacy of UVB treatment in 17 patients clinically but also showed, by obtaining skin biopsies before and after therapy, a reduction in skin phosphorus following UVB treatment to values that were comparable with those of patients with nonpruritic uremia or healthy volunteers [77]. Further investigation has been performed using narrowband UVB phototherapy, as most of the data on UV radiation have been predominately derived from studies using broadband UVB [80]. The results showed the effectiveness of narrowband UVB, as 9 of 15 patients with UP were marked as responders; however, remission was not prolonged, as 4 of 6 responders who came back for a follow-up had a recurrence [80,81]. Due to the carcinogenic effect of UVB, ultraviolet A (UVA, wavelength 315- 400 nm), which is safer than UVB, was studied for its efficacy, however, UVA did not demonstrate any benefit [82]. Narrowband UVB, which is generally accepted to be less carcinogenic than broadband UVB, should be a better alternative treatment in both efficacy and safety aspects.

4.5. Acupuncture and Electrical Needle Therapy

Modern medicine tries to explain the efficacy of acupuncture by describing its effects on the receptors of the nervous system, its action on the endogenous endorphin enkephalin and 5-hydroxytryptamine (5-HT), or that it can increase the number of leukocytes and strengthen the defensive mechanisms of the body [83]. Some studies show the benefit of acupuncture for UP. The fundamental information indicated that pruritus was transmitted by conductive C fibers, and acupuncture generates impulses that are carried by the smaller, myelinated, and rapidly conductive beta and delta fibers, all of which reach the spinal cord. There, opiate-like substances are released that block the slower C fiber impulses [84].

Acupoint injection, at San Yin Jiao (SP6), Xuehai (SP 10), Zusanli (ST 36) and Quchi (LI 11) acupoints, has been reported to be effective in UP [85]. Using a transcutaneous electrical nerve stimulation (TENS) acupressure apparatus at those points also showed a benefit in reducing UP [86]. Duo also reported that an electric needle is effective at two similar points (Quchi and Zusanli) [87]. Che-yi *et al*. also reported that acupuncture at the Quchi (LI 11) acupoint, which is close to the hemodialysis needle puncture site but not too close for acupuncture there to interfere with hemodialysis, is also effective for relieving UP [1]. However, acupuncture does not change the level of biochemical parameters associated with the development of UP—including magnesium, iPTH, phosphate and calcium.

4.6. Thermal Therapy

Hsu *et al*. investigated the effects on UP of 40 degree Celsius thermal therapy with far-infrared rays at the Sanyinjiao acupoint for 15 minutes and found a large decrease in pruritus scores in

the thermal therapy group compared with the non-thermal therapy group, even though there was no significant differences between groups [88]. The result implied that thermal therapy may have therapeutic benefits for UP.

4.7. Sauna

Stimulation of the sweat glands with a sauna has shown benefits, perhaps through augmented excretion of hypothetical pruritogen [89]. However, such treatment may cause major complications in fluid balance due to unquantifiable insensible water loss.

5. Topical Treatments

Topical treatment with skin emollient contained high water to hydrate stratum corneum is considered as a primary therapy for UP in CKD patients. In order to avoid any allergic reaction, emollients without perfumes or other additives is preferable [43,90].

5.1. Skin Emollients

Because xerosis plays at least an adjuvant role in the development of UP, emollients are a mainstay in the treatment. It has been suggested by several researchers that the use of emollients with high water content should be the first-line treatment [91,92]. The benefit of using emollients to treat dry skin in patients with UP has been reported by Morton et al. and others [9,43,93]. A pilot study on the use of urea 10% lotion with dexpanthenol, a moisturizer, showed significant improvement in skin itch [20]. The study by Balaskas *et al.* of 100 patients using glycerol and paraffin, showed a 75% improvement in UP and hence quality of life (p<0.001) [94]. The addition of endocannabinoids to creams containing structured physiological lipids demonstrated good efficacy and tolerance in a clinical study [61,95].

5.2. Sericin Cream

Sericin, a biopolymer with a high molecular weight, is a water-soluble protein that is obtained from the silkworm (*Bombyx mori*). Sericin is characterized by the presence of 32% serine, which is the main amino acid of the natural moisture factor (NMF) in human skin; therefore, sericin has excellent moisturizing properties that may be helpful for treating hypohidrosis. Sericin also demonstrates many biological activities and has been widely studied for potential use in medicines and biomaterials [96-100]. Moreover, sericin can significantly decrease the levels of the pro-inflammatory cytokines TNF-α and IL-1β in sericin-treated wounds in rats 7 days after an injury, compared with the levels found in normal saline-soaked wounds and cream base-treated wounds [101]. As previously mentioned, the immune-inflammatory hypothesis considers UP a dermatologic manifestation of chronic inflammation and treats the condition as a possible result of derangements in the immune system that are based on a pro-inflammatory pattern. Based on this reasoning, sericin was investigated for relieving UP. An in-subject,

randomized, double-blind, placebo-controlled experimental study was designed to investigate the effects of sericin cream (concentration 8%) versus the cream base (placebo) applied twice daily for 6 weeks in reducing the symptoms of UP (itching, dryness and redness) and skin pigmentation in 47 subjects with stable maintenance hemodialysis [102]. The results showed that sericin reduces pruritus in patients with UP. The use of sericin cream significantly increased the level of skin hydration after 6 weeks of treatment compared to baseline and to the use of the cream base. The use of sericin cream also significantly reduced the level of skin irritation and pigmentation after 6 weeks of treatment compared to baseline, while use of the cream base reduced skin pigmentation slightly but not significantly. Patients' quality of life was also assessed using the Thai version of the KDQOL-SF Version 1.3, and the results showed a better quality of life in all of the measured domains, including sleep and mood/emotional distress after the treatment period. When the mean score on the enrollment day was compared with the mean score on the day after the completion of treatment, significant differences were found in some domains, including pain, the symptoms/problems list in kidney disease, the effect of kidney disease on daily life and sleep, the most relevant parameter for itching. The overall score increased from 60.00 at the time of enrollment to 61.95 after 6 weeks of treatment, although this difference was not statistically significant. The results of this study suggest that sericin cream may be a good choice for treating pruritus in hemodialysis patients. Because sericin is obtained from natural sources that have high biocompatibility, it may cause fewer allergic reactions and lower resistances compared to other chemical substances.

5.3. Capsaicin

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide), an extract from capsicum or common pepper plant, can be used as a main ingredient in cream for the treatment of painful disorders including postherpetic neuralgia, cluster headaches, diabetic neuropathy, osteoarthritis and phantom limb [103,104]. Capsaicin blocks pain and itching by depleting and preventing the re-accumulation of substance P from local type C sensory nerve terminals [89,104]. After using 0.025% capsaicin cream for the treatment of UP in long-term dialysis patients, the results indicated that significant alleviation of pruritus was found with no serious adverse reaction [105,106]. Although topical capsaicin might be useful for the treatment of localized disease, it is impractical for large areas or generalized pruritus.

5.4. Tacrolimus

Tacrolimus is an immunomodulator targeting mainly at the T helper cells. It blocks the differentiation of Th1-type lymphocytes, and therefore, suppresses the production of IL-2. Due to these mechanisms, it was suggested that it might be beneficial in the treatment of UP. An observational study of 3 cases of severe UP in patients on peritoneal dialysis indicated a short-term efficacy of 0.03% tacrolimus ointment over 7 days. However, the use of this agent was not extended longer because of the potential carcinogenic effect of systemic tacrolimus [107], which resulted in an FDA black-box warning that was issued in 2006 against the prolonged topical use of tacrolimus creams and ointments. Nevertheless, some studies failed to demonstrate any efficacy of the topical calcineurin inhibitor in patients with UP [108,109].

6. Systemic Treatments

6.1. Opioid Antagonists

Endogenous opioids have been implicated in the genesis of the pruritus associated with cholestasis [110,111]. One study demonstrated the effect of naltrexone 50 mg/day for a week in 15 dialyzed patients with severe UP in a randomized cross-over trial, and the results indicated that short-term amelioration of UP was found and attributed to the inhibition of basophil histamine release. Only mild upper gastrointestinal tract symptoms were found to be the side effects [112]. Opioid antagonists should therefore be considered for patients with severe and persistent UP [2].

More recently, another perspective was elaborated on 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 [64]. A meta-analysis approach was used to assess the efficacy of nalfurafine, which is a κ-agonist, in two randomized placebo-controlled clinical studies. Nalfurafine was administered intravenously postdialysis over 2-4 weeks, and the results were encouraging, as improvements in the worst itching, itching intensity and sleep disturbances were noted in the nalfurafine group, with significant *p* values [113]. In addition, the evaluation of adverse events demonstrated that nalfurafine was well tolerated.

6.2. Erythropoietin

De Marchi *et al*. studied the effect of erythropoietin in dialysis patients with elevated plasma histamine levels in a placebo-controlled, double-blind, crossover study. They found that erythropoietin improved UP and decreased plasma histamine concentrations. Further, they found that it can result in marked improvement of UP and that recurrence of pruritus occurred after discontinuation of erythropoietin [114]. However, this effect was not related to the change in hemoglobin levels [115].

6.3. Serotonin Antagonists

Serotonin has been suggested as a possible mediator of cholestasis and UP. One study indicated that ondansetron, a selective inhibitor of serotonin type 3 receptors, at 4 mg twice a day for approximately 3 months can significantly reduce the severity of UP in peritoneal dialysis patients with moderate to severe pruritus [116]. This treatment was well tolerated and showed no significant side effects. However, the study by Ashmore *et al*. failed to show any significant change in the pruritus scores in patients treated with ondansetron in comparison with the placebo group [117].

6.4. Gabapentin

Gabapentin, a γ-aminobutyric acid analog, is a potent anticonvulsant drug that was has been clearly demonstrated as effective in the treatment of neuropathic pain, especially diabetic neuropathy. Considering that neuropathic pain and pruritus share common pathogenic

mechanisms, gabapentin, which is usually used to treat neuropathic pain, emerged as another possibility in the arsenal of treatment for severe UP resistant to other therapies [64]. Recent, limited data suggest that gabapentin is a promising drug in treating UP, given its efficacy and its safety [13,91,118]. In a randomized, placebo-controlled, double-blind study, 25 patients were treated with gabapentin versus a placebo for 4 weeks; the treatment was then reversed, and the mean pruritus score dropped significantly. No patient dropped out due to adverse events from gabapentin [119]. Regarding its pharmacokinetics, gabapentin is eliminated primarily through the kidney, and it is removed by hemodialysis. It has a significantly longer half-life in patients on hemodialysis than in those with normal kidney function, and thus, these patients need lower doses at less frequent intervals [64]. The recommended dose for hemodialysis patients is 200- 300 mg after each hemodialysis session, with somnolence, dizziness and fatigue being the most commonly reported side effects [120].

6.5. Antihistaminic Agents

Despite the fact that histamine might be implicated in the pathogenesis of UP and the demonstration of elevated histamine levels in patients with ESRD with pruritus [91,121], classical antihistamines showed very limited efficacy in the treatment of UP [53,54,94,121]. The response to the administration of antihistaminic agents is marginal, at best [9]. Mast cell stabilizers including ketotifen, 2-4 mg per day for 8 weeks, [55] and cromolyn sodium [55], however, were demonstrated to be effective in case series.

6.6. Long Chain Fatty Acids

Abnormalities in the plasma composition of essential fatty acids may be related to the etiology of pruritus in patients undergoing hemodialysis. After administration of 6 grams of ethyl ester of either fish oil, olive oil or safflower oil in double-blind study of 25 hemodialysis patients, the results indicated that pruritus was significantly improved due to the altered plasma fatty acid profile and increased prostaglandin E_2 (PGE_2) plasma concentration [122]. Another study indicated that the improvement in pruritus was due to an increase in PGE_1 plasma levels [123] after administration of γ-linoleic acid-rich evening primrose oil 2 grams per day for 6 weeks.

6.7. Lidocaine and Mexiletine

Parenteral administration of lidocaine, a membrane-stabilizing antiarrhythmic agent, can relieve pruritus in double-blind study however, significant side effects such as hypotension and grand mal seizures were found [124]. An oral dosage form of mexiletine, a longer half-life and less toxicity than lidocaine, was found to be ineffective for the treatment of UP [125].

6.8. Low Protein Diet

Low protein diet has been proposed for the treatment of UP due to the rational of less accumulation of renally excreted pruritogen [126]. However, low protein diet may lead to malnutrition which can be dangerous in CKD patients and detoxification showed no benefit on pruritus [2].

6.9. Oral Activated Charcoal

With the rationale of adsorbing an unidentified pruritogen, oral activated charcoal at the dose of 6 grams per day has been used for uremic pruritus. A double-blind crossover trial and a single-blind study have yielded impressive results [127,128]. This preparation is effective, inexpensive, and has a favorable side effect profile. However, this treatment has not yet been accepted and utilized in clinical practice [127,128].

6.10. Cholestyramine

The success of cholestyramine in treating PU is inconsistent. When administered at a dose of 5 grams twice a day, the gastrointestinal side effects are normally found. Moreover, the risk of acidosis must also be taken into consideration, particularly in patients who are not on dialysis [128,129].

6.11. Heparin

Patients on hemodialysis may develop pruritus when treated with porcine or bovine heparin. Pruritus is relieved promptly when another form of heparin is used, implying that these heparins act as allergens [9]. Paradoxically, administration of heparin at 75- 100 mg twice a day for 2-3 weeks can improve UP in some dialysis patients [130]. From the mechanism of action by inhibition of T-lymphocyte heparanase activity which is an important factor for T-cell migration to target tissues, low molecular weight heparin such as enoxaparin at low dose is effective in treating pruritus associated with lichen planus [2,131].

6.12. Thalidomide

Thalidomide is a relatively selective inhibitor of TNF-α production. The study indicated that thalidomide at 100 mg per day administered for 1 week can significantly reduce the intensity of pruritus by up to 80% in more than half of the subjects, suggesting a potential role for this agent in the treatment of persistent UP [132].

6.13. Nicergoline

Nicergoline is a dopamine receptor agonist and a partial α-adrenergic blocker related to ergot alkaloids. A double-blind, placebo-controlled study that investigated the effect of 30 mg per day by mouth and 5 mg per day intravenously during dialysis, indicated relief of pruritus in most patients, and the effect lasted for 24- 48 h with improvement persistent in long-term therapy (30 mg per day) in most patients who responded to the initial treatment [133].

6.14. Nicotinamide

Nicotinamide is the pyridine-3-carboxylic acid amide of niacin, a component of the vitamin B complex. Namazi *et al*. suggested 3 mechanisms through which nicotinamide can be effective in treating UP: the anti-inflammatory effect through the inhibition of the expression of major

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histocompatibility complex (MHC)-II and the production of IL- 12, TNF-α and IL-1; the inhibition of cyclic adenosine monophosphate (cAMP) phosphodiesterase and stabilization of mast cells and leukocytes and hence, blocking histamine release; and the increase of the biosynthesis of ceramides by keratinocytes with the resultant alleviation of xerosis [134]. For those reasons, nicotinamide could be an effective treatment for UP. However, clinical trials should be conducted to confirm its efficacy.

7. Conclusion

UP is one of the most common and disabling symptoms for patients with ESRD. It is considered to be an inflammatory systemic disease rather than a local skin disorder. Biomarkers of inflammation are increased in patients with UP, and an imbalance of the endogenous opioidergic system might be involved in the complex pathogenesis of the disease. UP affects up to 90% of patients on dialysis and is associated with a high morbidity and mortality. Given the complexity of its pathogenesis and the lack of clear evidence regarding the efficacy of more conservative therapies, the only definitive treatment is kidney transplantation.

Antihistamines, which are the most widely used antipruritic agents, are ineffective for the treatment of hemodialysis-related pruritus. Safe and effective modalities, and those that should probably be considered as first-line treatment, are topical emollients. Other physical therapies and medications should be further investigated due to the inconsistent trial results. Without definitive treatment of the underlying disease, therapy for hemodialysis-related pruritus is often palliative at best, aiming to minimize the severity of pruritus and to improve the quality of life.

The standard of care remains to optimize the dialysis dose and to use biocompatible membranes, as well as the treatment of mineral abnormalities and anemia. The reasonable course for treating hemodialysis-related pruritus should be as follows:

a. If the patients can tolerate it, dialysis should achieve a K_t/V_{urea} value greater than 1.4.

b. If the patient is sensitive to ethylene oxide or the dialysis membrane, a gamma-irradiated or noncomplement-activating membrane should be used.

c. Compliance with dietary restrictions and phosphate-binding therapy should be encouraged.

d. Epoetin alpha therapy should start at 36- 360 units/kg intravenously or subcutaneously weekly and be optimized according to hemoglobin and hematocrit values.

e. Topical emollients should be started if the symptoms persist and followed by step therapy in Figure 1.

Without definitive treatment of the underlying disease, therapy for hemodialysis-related pruritus is often palliative at best, aiming to minimize the severity of pruritus and to improve patients' quality of life.

Author details

Pornanong Aramwit[1*] and Ouppatham Supasyndh[2]

*Address all correspondence to: aramwit@gmail.com

1 Bioactive Resources for Innovative Clinical Applications Research Unit and Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, PhayaThai Road, Phatumwan, Bangkok, Thailand

2 Division of Nephrology, Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand

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