Itching in renal failure: a curse with a cure

Uraemic pruritus, or renal itching, is a common and distressing problem for people with renal failure. It is even associated with increased mortality. There is now quality evidence supporting the use of gabapentin and pregabalin for the treatment of severe itching in renal failure through a stepwise approach, as Hugh Rayner explains.

Hugh Rayner
Consultant Nephrologist, Heart of England NHS Foundation Trust
hugh.rayner@heartofengland.nhs.uk

Itching in renal failure: a curse with a cure

Uraemic pruritus, or renal itching, is a common and distressing problem for people with renal failure (NHS Media Hub, 2012a). When severe, it leads to sleep deprivation, depression and is associated with an increased risk of death. Fortunately, there is now good trial evidence and extensive experience to guide effective treatment, which can transform the lives of affected patients (NHS Media Hub, 2012b). Renal nurses play an important role in identifying those patients affected and helping them get the right treatment. This article sets out the existing knowledge about the condition and offers a simple stepwise approach to management.

Some degree of itching is common in patients with advanced kidney failure. About 10% of haemodialysis patients report being extremely bothered by itching (Figure 1) (Pisoni et al, 2006). If these numbers seem surprisingly high this is because many patients do not report itching unless they are asked.

The itching is likely to be related to renal failure rather than a separate skin disease if patients have no obvious rash other than the marks caused by scratching. In severe cases, hard itchy nodules can develop (prurigo nodularis), which break through the skin when scratched.

Itching due to renal failure is different to the common symptom that most people experience. The sensation is characteristically described as being underneath rather than in the skin (NHS Media Hub, 2012a). Patients often say they feel like ‘tearing their skin off’ to get at the itch.

It is commonly felt on the back, limbs and scalp. The site of the itching can move around the body and varies in intensity from day to day (Mathur et al, 2010). It is worse in warm environments; some patients find relief by cooling themselves with wet towels or going outside into the cold.

When itching is severe and persistent, patients are likely to become exhausted and depressed (Figure 2) (Pisoni et al, 2006). It is commonly worse at night when patients are warm in bed, which makes it difficult to get off to sleep and can greatly reduce sleep quality. Sleep disturbance is linked to a significantly increased risk of mortality in patients with moderate or severe itching (Pisoni et al, 2006).

Possible mechanisms of uraemic pruritus

Calcium and phosphate hypothesis

It is commonly noted that some patients with severe hypercalcaemia or hyperphosphataemia report itching that resolves when the levels return towards normal. Furthermore, there is a statistically significant association between increased calcium and phosphate levels and the risk of having severe itching (Pisoni et al, 2006). An old study showed that increased levels of calcium, phosphorus and magnesium in skin tissue in patients with severe itching were reduced after phototherapy, which also reduced itching (Blachley et al, 1985).

However, the great majority of patients with severe itching have serum calcium and phosphate levels within the recommended range (Rayner et al, 2013). Also the average level of calcium and phosphate in patients severely affected by itching is only marginally higher than those that are not (Pisoni et al, 2006).

These data suggest that, for most patients, raised calcium and phosphate levels is usually not the cause of itching. They may be associated through a link with another causative factor. The widely held view that itching is usually caused by poor compliance with dietary restrictions or phosphate binders is not supported by the evidence. Patients may adopt an extreme diet in a vain attempt to lower their phosphate and stop the itching (NHS Media Hub, 2012a). Self-blame adds to the
Depression caused by the constant irritation and sleep deprivation.

**Histamine hypothesis**

The typical itch associated with an allergic reaction (e.g. ‘hives’ or urticaria) or insect bite is mediated by histamine in the skin. Plasma histamine levels are increased in renal failure suggesting that they may mediate symptoms of itching. However, there is no correlation between the levels of histamine and the symptoms of itching (De Filippi, 1995).

Antihistamines are commonly used to treat renal itch. However, there has been no well-conducted placebo controlled trial demonstrating that antihistamines are effective for renal itching.

**Central nervous system hypothesis**

The hypothesis that is most strongly supported by evidence is that itching is a manifestation of abnormal central nervous system functioning due to uraemia. Patients with renal failure experience a variety of symptoms related to overactivity of the central nervous system: insomnia, restless legs syndrome, myoclonic jerking and epileptic seizures. Insomnia due to renal failure may be related to elevated levels of the neurotransmitter chemical linked to arousal—the incretins (Rayner, 2003). These mediate the activation of pathways in the central nervous system. Itching may be another manifestation of these nervous system imbalances.

Gabapentin and pregabalin are drugs conventionally used to treat epilepsy and neuropathic pain. They work by inhibiting voltage-gated calcium channels in nerve cell membranes in the brain. Gabapentin has been shown to dramatically reduce the severity of renal itch in placebo controlled trials (Gunal et al, 2004; Manenti et al, 2005; Naini et al, 2007; Razeghi et al, 2009; Aperis et al, 2010; Solak et al, 2012). Patients report that the tablets have a rapid and clear-cut effect; about 2 hours after taking the tablet the itching stops ‘like a light switch’ (NHS Media Hub, 2012b). The drugs also significantly improve sleep quality in patients with insomnia due to renal failure, with and without itching (Biyik, 2012). The remarkable effect of these drugs indicates that they are not damping down neural activity in a non-specific way. They seem to have a specific effect on the neural pathways that mediate renal itching.

Further support for a central nervous system mechanism comes from the effect of drugs that act on opioid receptors in the brain. It is thought that the ‘mu’ opioid system is itch-inducible, whereas the ‘kappa’ system is itch-suppressive. Dialysis patients given oral naltrexone (a ‘mu’ and ‘kappa’ opioid-receptor antagonist) (Peer et al, 1996) or nalfurafine (a selective kappa-opioid receptor agonist) (Kumagai et al, 2010) in placebo controlled trials showed a significant reduction in itching. However, the benefit of naltrexone has not been confirmed in a more recent trial (Pauli-Magnus et al, 2000). The relief of itching with nalfurafine was not as complete in the long term as found with gabapentin (Wikström et al, 2005; Kumagai, 2012).

---

Figure 1. The frequency of itching in patients on haemodialysis (Pisoni et al, 2006)
Treatment of itching in patients with renal failure

A stepwise approach to the treatment of renal itching is recommended. It is helpful to ask patients to grade the severity of their itching using a score out of 10, where 0 is no itching and 10 is the worst itch imaginable. Patients who are sufficiently bothered by itching to take regular medication usually report a severity of 6 or more out of 10.

Step 1: review serum calcium and phosphate
Review serum calcium, and phosphate and, for dialysis patients, treatment adequacy. Try to correct these if they are significantly outside the recommended range. However, symptomatic treatments should be given while these corrections are being attempted. Patients may adopt an extreme diet in a vain attempt to lower their phosphate and stop the itching. The self-blame adds to the depression caused by the constant irritation and sleep deprivation.

Step 2: topical emollients
Moisturising cream is helpful to reduce the drying of skin (xerosis) that is common in renal failure. Crotamiton cream (Eurax), which is also used to treat scabies, may be effective. Cream rich in gamma linolenic acid (GLA) may be helpful (Chen et al, 2006).

Step 3: antihistamines
Try antihistamines for mild or moderate itching. They are relatively free of side effects and available over the counter. However, there have been no well-conducted clinical trials demonstrating that antihistamines are effective for renal itch. Any effect they do have is most likely due to their sedative effect, which may help patients get off to sleep at night. If they do not give effective relief after a week or two, progress to the next step.

Step 4: gabapentin
Gabapentin or pregabalin reduces itching severity from 8/10 to 1/10 in 85% of severely affected patients (Rayner et al, 2013). Try low-dose gabapentin for moderate or severe persistent itching (>6 out of 10 severity). Patients should be given 100mg daily or after each haemodialysis treatment, taken at night. Patients should be advised that this is effective in two out of three patients. One in three have intolerable side effects,

Figure 2. The association between itching and depression in patients on haemodialysis (Pisoni et al, 2006)
Itching is common in patients with chronic kidney disease and on dialysis. Ask patients about itching—they often do not mention it. Gabapentin or pregabalin reduces itching severity from 8/10 to 1/10 in 85% of severely affected patients. Patients should be advised about side-effects of gabapentin and the drug initiated at a low dose. Patients intolerant of gabapentin, usually due to excessive drowsiness, may tolerate pregabalin.