Uremic Pruritus: An Itch with Ominous Consequences

Michael J. Germain

Baystate Medical Center, University of Massachusetts Medical School, Springfield, MA, USA

Pruritus is a common and a distressing symptom in patients with chronic kidney disease. The most recent epidemiologic data from the Dialysis Outcomes and Practice Patterns Study [1] suggest that approximately 40% of patients with end-stage renal disease experience moderate to severe pruritus and that uremic pruritus (UP) has a major clinical impact because it is strongly associated with poor quality of life, impaired sleep, depression, and increased mortality [1]. The Dialysis Outcomes and Practice Patterns Study is an international longitudinal study of dialysis patients that has been in practice since 1995. International qualitative research has consistently shown that patients' rate symptom relief at the top of what they would like addressed both in clinical practice and research [2].

It is likely that uremic toxins are the proximate cause of UP and it is also probable that using an effective method of removing uremic toxins with efficient dialyzers could be the reason behind the modest decrease in the incidence of UP. Dialysis intensification (more frequent and/or longer dialysis treatments) can improve UP and replacement of renal function with a kidney transplant will cure UP. Underrecognition and treatment continue

to be a consistent finding [3]. The pathophysiology of UP remains largely unclear, though preliminary data point to several hypotheses including increased systemic inflammation [4]; dysregulation of serum PTH, calcium, and phosphorus levels (there is poor evidence that this is the pathophysiologic mechanism, and treatment of hyperparathyroidism and/or hyperphosphatemia has not been shown to improve UP). UP can present somewhat variably, though it tends to affect large, discontinuous, but symmetric areas of skin and is found to be most symptomatic at night. Data for therapy specifically for UP remain limited although intake of topical capsaicin and gabapentin, UVB phototherapy and acupuncture have been reported to be effective in small trials.

Kappa opioid receptors do mediate the intensity of itch, and nafurafine (a kappa opioid receptor agonist) has been demonstrated to be effective in alleviating UP and it is available for use in Japan [5]. Naloxone (a mu-opioid receptor antagonist) has also been shown to be effective in the treatment of UP.

In this issue of the journal, Mathur et al. [6] have reported the efficacy and safety of nalbuphine as an extended release formulation in the treatment of UP in hemodi-

alysis patients. Nalbuphine is a kappa-opioid antagonist and a mu-opioid agonist. This combined mechanism of action has an advantage in that it has a low addiction potential. The study is remarkable for its rigorous study design and validated measures adopted to alleviate itching. These measures were validated in dialysis patients in an observation study of UP in 2010.

The Patient Assessed Disease Severity is an easy and a validated tool that is quite practical to use in clinical practice; patients are asked to self-categorize their itching levels as “A”, “B”, or “C” [5]. Mathur et al. [7] used this simple tool to screen patients for inclusion in the study. As a primary outcome measure, they used the patient reported outcome (PRO) measure of itching intensity on a Numerical Rating Scale, the secondary outcomes Skindex-10, itching-related sleep disruption (using the Itch Medical Outcomes Study), and the Hospital Anxiety and Depression Score. All these PRO measures have been specifically validated in UP [7]. This study shows that PROs can be as

rigorous an outcome measure as lab tests and other “hard” measures. In fact, in a condition such as UP or pain, the PRO is the hard measure, since pain is only what the patient experiences and there is no “objective” way to measure pain. This is hard for many scientists and physicians to accept because they are used to measuring variables in a controlled lab setting. This study demonstrates that science can be rigorously researched only with PROs.

Other novel medications are currently being studied for UP, including a peripherally restricted kappa opioid agonist and an NK-1 antagonist.

We are now approaching a time when we nephrologists will have effective and safe approved treatments for UP, a condition associated with severe morbidity and mortality. Now we need to start using PROs rigorously and routinely in the dialysis unit instead of just focusing on lab values that have little impact on patient well-being. This is what patients have told us is important to them and we should pay attention to it.

References

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