Clinical Note

Mirtazapine for Pruritus

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Abstract
Pruritus is a relatively rare but distressing symptom associated with cholestasis, renal failure, and
malignancies. Medical management recently has included the use of ondansetron and paroxetine.
We report four patients whose pruritus responded to mirtazapine. J Pain Symptom Manage
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Key Words
Pruritus, mirtazapine, cholestasis, renal failure, lymphoma

Introduction
Pruritus (itching) is an unpleasant sensation, which can vary in severity ranging from mild to
tormenting. It will elicit the urge to scratch, which temporarily decreases pruritus. Pruritus
may be seen as a minor, even humorous, disability but it can be severe enough to cause abject misery. In addition to a social embarrassment, the itch-scratch-itch cycle damages skin integrity, decreases resistance to infections, and impairs the quality of life.

The physiological basis of pruritus includes multiple mechanisms that are rather protean. The neural transmission associated with pruritus follows the same pathway as pain, even though the sensation is unique. Pruritus is initiated by stimulation of unmyelinated C-fibers in the dermal-epidermal junction. Mediators of pruritus include histamine through H1 receptors, and serotonin through 5HT2 and 5HT3 receptors. The actual sensation may depend on special temporal patterns of neural excitation and location of receptors. The perception of pruritus leads to a motor response of scratch which stimulates myelinated A delta sensory fibers and temporarily block the sensation. Because the physiology of pruritus is complex, similar to pain, much of the underlying mechanisms are poorly understood. It is therefore a challenge to find an effective medication to manage severe pruritus.

A variety of agents have been used to treat itch. The most popular are antihistamines. Recently, opioid antagonists, the serotonin receptor blocker ondansetron, and the selective serotonin reuptake inhibitor (SSRI) paroxetine are playing an increasingly important role in the management of pruritus. Antihistamines frequently are not helpful with cholestatic pruritus, pruritus associated with renal failure, or paraneoplastic pruritus. Selective serotonin reuptake inhibitors (SSRIs) are helpful in the itch associated with myeloproliferative disorders. Paroxetine relieves paraneoplastic, opioid, and cholestatic pruritus. The Harry R. Horvitz Center for Palliative Medicine is a World Health Organization Demonstration Project in Palliative Medicine.

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antagonists (i.e., parenteral naloxone, or oral naltrexone) can relieve cholestatic pruritus. Ondansetron relieves cholestatic, opioid, and renal failure associated pruritus.\textsuperscript{9,11,14} Ondansetron is expensive and SSRIs, although less expensive, are associated with significant drug–drug interactions and adverse drug effects. Opioid antagonists will reverse analgesia and are contraindicated in hepatic failure.

The antidepressant mirtazapine, an H\textsubscript{1}, 5HT\textsubscript{2b}, and 5HT\textsubscript{3} receptor blocker, may be an effective alternative treatment for pruritus arising from cancer, cholestasis, and renal failure. We report four cases to illustrate its potential therapeutic role.

**Case One**

A 62-year-old African-American man presented with an adenocarcinoma of unknown origin and multiple liver metastases with jaundice. He was admitted to the acute palliative medicine unit from home, where he was receiving hospice care. The admission was for symptomatic hypercalcemia, which was appropriately treated. For pruritus, the patient had received oral hydroxyzine 50 mg every 6 hours as needed for at least two weeks prior to admission. The pruritus was unresponsive to this treatment. Naloxone and ondansetron had been considered previously, but were never administered.

The hypercalcemia resolved with pamidronate and calcitonin, but the pruritus failed to improve. Eight days post-hospitalization, the hospice nurse called requesting treatment for his generalized pruritus, which had become so severe that it kept him up throughout the night. Mirtazapine 15 mg at night was initiated. Within 24 hours, the pruritus completely subsided and he was able to sleep uninterrupted through the night. His jaundice remained unchanged and although he died from liver metastasis several weeks later, the pruritus did not return. Mirtazapine was continued at the same dose until his death.

**Case Two**

A 77-year-old African-American woman with Stage III-B nodular sclerosis Hodgkin’s disease was diagnosed 18 months prior to her hospitalization on the palliative medicine unit. Her diagnosis was accompanied by paraneoplastic pruritus, for which she sought help from several physicians. A diagnosis of advanced Hodgkin’s disease was made and she received standard chemotherapy. She had a complete remission but relapsed six months later. She then underwent an autologous bone marrow transplant with a second remission. Her remissions were associated with remission of her pruritus. She was admitted to the oncology service in January 2002 with generalized weakness, shortness of breath, pleural effusions, peripheral edema, and progressive pruritus. A bone marrow biopsy demonstrated recurrent disease and she was transferred to the inpatient palliative medicine unit. She was started on mirtazapine 15 mg at night. Within seven days, the pruritus improved 75%, (she was asked if her pruritus was relieved “not at all, by 25%, 50%, 75% or 100%.”) Her medication was increased to 30 mg at night and by the time of discharge from the palliative medicine unit during the last week of January 2002, the pruritus had completely resolved. She continued on mirtazapine at home under hospice care.

**Case Three**

An 80-year-old African-American man with a history of chronic lymphocytic leukemia that transformed to a large B-cell lymphoma presented to the palliative medicine unit with edema, ascites, retroperitoneal adenopathy, and moderately severe pruritus. He had no clinical evidence of cutaneous lymphoma. His admission to the acute palliative medicine program followed one cycle of cyclophosphamide, vincristine, prednisone, and rituximab. He had moderate chronic renal insufficiency and a computerized tomographic scan demonstrated retroperitoneal adenopathy without hydronephrosis. The pruritus was severe enough that he sought treatment. He was started on mirtazapine 15 mg at night. Within two days, his pruritus improved 80%. It completely resolved on 30 mg at the time of his dismissal the last week of January 2002. A course of palliative radiation to his retroperitoneal disease was started during hospitalization. His pruritus resolved before completing radiation. He was continued as an outpatient on 30 mg of mirtazapine and weekly rituximab.
Case Four

A 64-year-old Caucasian man with advanced renal cancer post-nephrectomy developed pruritus from renal failure. His creatinine was 5.2 mg/dL, which had risen over six months due to progressive metastasis to his remaining kidney. In October 2001, he was transferred to the acute palliative medicine service with mild confusion, bone pain, and severe pruritus. His bone pain resolved with methadone, but his pruritus remained a major problem. He was placed on mirtazapine 7.5 mg at night for sleep and ondansetron 8 mg every 6 hours for pruritus, which produced a partial response. Mirtazapine was increased to 15 mg at night in November 2001 and to 30 mg in December 2001. His pruritus resolved with 30 mg of mirtazapine, which allowed discontinuation of ondansetron without relapse of his pruritus. Mirtazapine was continued until his death during the first week of February 2002.

Discussion

Histamine causes pruritus either through direct skin contact or by intradermal injection. The H1 receptor is one of the main initiators of pruritus and regional mast cells are responsible for histamine release.3 Serotonin acts directly on peripheral neuronal serotonergic receptors, which are 5HT2 and 5HT3 subtypes. Endogenous or exogenous opioids will produce pruritus from peripheral histamine release or by central serotonergic pathways.3 Dialysis patients and persons suffering from liver failure or cholestasis have elevated circulating plasma serotonin levels assumed to be responsible for pruritus.3,4,6

Major causes of pruritus are renal failure, liver failure, cholestasis, and malignancies. Itch is a paraneoplastic syndrome usually associated with Hodgkin’s disease and much less so with non-Hodgkin’s lymphoma.5 Solid tumors will occasionally produce generalized pruritus unrelated to liver or renal dysfunction. Iron deficiency and thyroid disease will cause pruritus in a minority of patients.3

Mirtazapine is the first of a new class of antidepressants which are selective noradrenergic and specific serotonin receptor antagonists.15,16 Mirtazapine facilitates norepinephrine neurotransmission and selectively increases serotonin neurotransmission by blocking central presynaptic alpha-2 adrenoreceptors (auto-receptors) and alpha-2 adrenoreceptors on serotonergic neurons (heteroreceptors).16 In addition, it blocks postsynaptic 5HT2 and 5HT3 receptors, reducing serotonin side effects and redirecting serotonin towards 5HT1A receptors. Mirtazapine also blocks H1 receptors, which accounts for sedation and perhaps weight gain.15,16 Mirtazapine has rarely been associated with nausea or initial anxiety, which often occurs with the SSRIs.15,16 Due to its pleiotropic cytochrome metabolism (CYP2D6, CYP1A2, CYP3A4) and lack of cytochrome inhibition, mirtazapine has few drug–drug interactions. It has a wide therapeutic index and can be used with other drugs with relative safety.15,16

Mirtazapine blocks most of the known major receptors associated with pruritus (i.e., H1, 5HT2, and 5HT3). In our experience, doses for relief of pruritus may be as low as 15 mg. Some patients require dose escalation. The cost is comparable to the SSRIs, less than ondansetron, but more than hydroxyzine. Mirtazapine is given once daily due to its long half-life, which improves compliance. It may also improve insomnia, anorexia, and depression, all of which are common in advanced cancer. Mirtazapine is associated with weight gain, which can be another advantage in cachectic patient. Dose reduction is unnecessary for patients with advanced liver or renal failure.

Mirtazapine is associated with sedation and weight gain as major side effects.15,16 Sedation is inversely related to dose, and tolerance can develop with ongoing therapy.15,16 Sedation is worsened with alcohol and benzodiazepines, and both should be avoided.

Conclusion

Mirtazapine may be an effective drug for pruritus associated with advanced cancer, cholestasis, and hepatic and renal failure. The mode of action is most likely to be related to binding to cutaneous serotonin and histamine receptors, though central receptor blockade may also play a role. Mirtazapine has several advantages over other medications, which makes it a reasonable choice for the treatment of pruritus.

References


