CASE REPORT

Ondansetron to Treat Pruritus Due to Cholestatic Jaundice

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Intractable itching is a symptom of cholestatic liver disease of various causes that is bothersome and difficult to manage. Although treatment of the primary cause of cholestasis is paramount in resolving the issue, given the debilitating consequences of pruritus, symptomatic treatment is frequently necessary. Although many medications including cholestyramine, rifampin, opioid antagonists (i.e., naloxone, naltrexone), phenobarbital, and antihistamines have been used to treat cholestatic-induced pruritus, none has resulted in uniform success. We report anecdotal success with the use of ondansetron to treat pruritus associated with cholestasis following prolonged intensive care unit course of a 16-year-old. The theories accounting for pruritus with cholestasis are presented, treatment options are reviewed, and the role of ondansetron in the treatment of pruritus is discussed.

INDEX TERMS cholestatic jaundice, ondansetron, pruritus

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INTRODUCTION

Intractable itching is a symptom of cholestatic liver disease of various causes that is bothersome and difficult to manage. It has been estimated to occur in up to 25% of patients with clinical jaundice.[1] Treatment with medications to hasten the resolution of the cholestasis and hyperbilirubinemia, such as ursodeoxycholic acid and cholestyramine, is based on the assumption that pruritus results from the cutaneous deposition of bile salts with subsequent irritation of nerve endings in the skin. This theoretical assumption is supported by data demonstrating an increased concentration of bile salts in the skin.[2,3] Furthermore, pruritus can be produced by the intradermal instillation of bile acid.[4] Although the exact pathogenesis of pruritus associated with cholestasis continues to be debated, given the debilitating nature of the symptom, treatment is necessary in many patients. We report the successful use of serotonin or the 5-hydroxytryptamine type 3 (5-HT_3) antagonist ondansetron to treat pruritus associated with cholestasis following the prolonged intensive care unit (ICU) course of a 16-year-old. Initial attempts to control pruritus with diphenhydramine, hydroxyzine, and a naloxone infusion failed. The theories accounting for pruritus with cholestasis are discussed, treatment options are reviewed, and the role of ondansetron in the treatment of pruritus is presented.

CASE REPORT

The patient was a 16-year-old, 82-kg male with chronic thromboembolic pulmonary hypertension who had a significant calcified clot present in the left and right pulmonary arteries. He was taken to the operating room for bilateral pulmonary endarterectomy and thrombectomy during cardiopulmonary bypass. Following the procedure, he was admitted to the cardiothoracic ICU (CTICU). The protracted postoperative course included the development of adult respiratory distress syndrome requiring 10 days of extracorporeal membrane oxygenation and 7 weeks of mechanical ventilation, eventually necessitating a tracheostomy. During his extended CTICU stay, he also developed renal failure requiring continuous renal replacement therapy that was transitioned to chronic hemodialysis. His lingering illness, multisystem organ failure, and a prolonged absence of enteral feeds resulted in cholestatic jaundice with a peak se-

rum total bilirubin concentration of 18.8 mg/dL (direct, 17.7 mg/dL). During his convalescence, he complained of constant and severe pruritus that failed to respond to intravenous dosages of diphenhydramine, up to 50 mg every 4 hours, to oral doses of hydroxyzine, 25 mg every 6 hours, and a naloxone infusion, starting at 0.25 mcg/kg/hr and subsequently increased to 1 mcg/kg/hr. When these agents failed to resolve the pruritus, a 4-mg intravenous or oral dose of ondansetron (GlaxoSmithKline, Philadelphia, PA) was administered every 4 hours as needed. Over the ensuing week, the patient received 1 to 2 doses of ondansetron per day with complete resolution of the pruritus. During the second week, the dose was increased to 8 mg every 4 hours as needed, as the patient's relief was not complete following the 4-mg dose. He continued to receive 1 to 2 doses per day, which provided prompt resolution of pruritus. As he resumed activities of daily living and tolerated enteral feedings, there was a progressive decline in the serum bilirubin values. By the end of the second week of therapy, no additional doses were needed as the bilirubin level had decreased to 4.2 mg/dL. The patient was eventually transferred to the rehabilitation wing of the hospital and then discharged home.

DISCUSSION

In simple terms, itching can be defined as an unpleasant sensation resulting in the desire or need to scratch.[5] The process of this sensation involves skin receptors, the peripheral nervous system, and specific regions of the brain and central nervous system.[6,7] Furthermore, as the perception of itch is highly subjective, it may vary from person to person. As itch has traditionally been a difficult symptom to classify and treat, various investigators have proposed systems of classification. In 2003, Yosipovitch et al.[7] and Twycross et al.[8] proposed a four-category characterization of pruritus that has become widely accepted. In their categorization, itch was divided into four categories: pruritoceptive, neurogenic, neuropathic, and psychogenic. Pruritoceptive itch is defined as a visible inflammatory process, with the itch sensation generated in the skin (e.g., from scabies and urticaria). Neurogenic itch is generated by the central nervous system in response to pruritogenic substances that are circulating in the blood stream (e.g., from pruritus associated with cholestasis). Physical lesions of the central or peripheral nervous system, including tumors or entrapment affecting the nerves involved in the itch sensation, cause neuropathic itch. Finally, psychogenic itch is a delusional process with no physical cause evident to explain the sensation.

Itch, pressure, and pain are closely related sensations, as shown by the alleviation of itching by scratching or rubbing the affected area. The sensation of both itch and pain are sensed by free nerve endings and transmitted through unmyelinated C fibers found in the epidermis and dermal–epidermal junction. Itch is thought to be transmitted through mechanoinsensitive nerve fibers, which ascend in the spinal cord via the contralateral spinothalamic tract to the thalamus. From the thalamus, there are third-order neuron projections primarily to the cingulate cortex. Other involved areas of the central nervous system include the supplementary motor area and the left inferior parietal lobe, which generate the sensation of itching and produce the action of scratching. Several mediators have been linked to the sensation of pruritus including histamine, acetylcholine, serotonin, tryptase, prostaglandin E, opioid peptides (both endogenous and exogenous), nerve growth factor, leukotriene B4, and cytokines.[5–7] This complex and multifactorial nature of pruritus can make the treatment of the symptom difficult, especially under conditions where the exact mechanisms have been not identified.

Pruritus associated with cholestasis can be particularly severe and debilitating.[9] The itch can be constant, frequently disrupting sleep, and in extreme cases may lead to thoughts of suicide. Severe pruritus in itself can even be an indication for liver transplantation.[9,10] Cholestasis-associated pruritus is highly refractory to treatment, causing severe disruption to the lives of patients suffering from this disease. As noted in our patient, pruritus was another confounding factor in his protracted stay in the ICU. The pruritus resulted in difficulties falling asleep and frequently awakening during sleep, was constant while he was awake and increased the usual sleep deprivation and disruption which is a chronic issue in the ICU setting. His pruritus was refractory to treatment with several agents including antihistamines, ursodeoxycholic acid, and opioid antagonists. Furthermore, adverse

effects were noted from the sedative effects of the antihistamines that were used as first-line therapy to treat the pruritus. With cholestasis, there is evidence that pruritogenic substances are formed in the liver and accumulate in the skin or the central nervous system, resulting in pruritus. This is shown by the alleviation of itch symptoms with the progression of hepatic failure as the failed liver is no longer able to produce the offending mediators.[9,10] However, confounding factors are present which need further investigation and explanation. The intensity of the pruritic sensation does not correlate with the severity of the cholestatic disease, and the perception of itch may differ from patient to patient. Mediators that have been implicated in the pathophysiology of cholestatic itch are bile acids, serotonin, histamine, and endogenous opioids. Although blood levels of bile acids are elevated in cholestatic disease and the intradermal injection of bile acids produces cutaneous pruritus, the levels of bile acid do not correlate to the level of itch. This poor correlation suggests that the bile acids may not be the primary mediator of the process but rather may induce the release of substances that cause pruritus.

Histamine is a substance commonly implicated in the pathogenesis of pruritus, and systemic histamine levels are elevated in patients with cholestatic disease. Interestingly, antihistamines are generally ineffective in alleviating pruritus associated with cholestasis.[9,10] The ineffectiveness of antihistamines for this indication has led to the search for other potential medications. Like bile salts, serotonin produces local pruritus when injected into healthy volunteers. Serotonin ($5\text{-}HT_3$) receptors are present on C fibers, which are known to be involved in the neural pathway of itching, as previously noted. Blood levels of endogenous opioids, specifically Met-enkephalin, are also increased in cholestatic disease. There is significant evidence that decreased clearance and excretion of endogenous opioids during cholestasis and hepatic insufficiency lead to the accumulation of these substances, which results in the sensation of itch. This is further supported by symptom alleviation with the administration of opioid antagonists.[11–13]

Medications used to treat cholestatic pruritus have included agents that target the central or peripheral mechanisms involved in pruritus (i.e., antihistamines), medications to decrease the severity of cholestasis by augmenting bile flow or binding bile acids within the gastrointestinal tract (i.e., phenobarbital, cholestyramine, ursodeoxycholic acid), medications that antagonize substances thought to be responsible for pruritus (i.e., naloxone, naltrexone, $5\text{-}HT_3$-antagonists), and rifampin, which is presumed to stimulate the hepatic microsomal enzymes 6-hydroxylation of bile acids, thereby facilitating their elimination.[10-14] Naloxone and opioid antagonists, when used in larger doses, may interfere with the provision of analgesia.[15] Antihistamines (e.g., diphenhydramine and hydroxyzine) are generally not effective in relieving pruritus. Additionally, they treat the primary symptom and not necessarily the cellular mechanisms responsible for the pruritus. Adverse effects as noted in our patient include sedation, alteration of the normal sleep cycle, and anticholinergic effects.

Ondansetron is a serotonin receptor antagonist that acts selectively at the $5\text{-}HT_3$ receptor.[16,17] It is used most commonly as an antiemetic agent in various clinical scenarios. It acts both peripherally at the vagal nerve and centrally in the chemoreceptor trigger zone. Ondansetron offers the option of several routes of delivery including oral, intravenous, and even sublingual/transmucosal delivery. The half-life is 6 to 7 hours in infants, 1 to 4 months of age; approximately 3 hours in infants and children 5 months to 12 years of age; and 3.5 to 5.5 hours in adults; thereby allowing dosing every 4 to 6 hours as needed. Ondansetron undergoes hepatic metabolism via glucuronidation and sulfate conjugation. The medication is well tolerated and has minimal side effects, even at large doses.[18] The most common adverse effects include diarrhea, headache, and mild increases in hepatic transaminase levels.

As noted above, one of the postulated mechanisms of cholestatic-induced pruritus involves the serotonin system. As a serotonin antagonist, ondansetron and other medications of this class (e.g., granisetron and dolasetron) have been used to treat pruritus associated with many different conditions including uremic pruritus and opioid-induced pruritus.[19–21] Additionally, several anecdotal reports outline the successful use of ondansetron and related agents in the treatment of pruritus associated with cholestasis.[22-25] As early as 1996, Schworer and colleagues[26] attempted to demonstrate the efficacy of ondansetron in treating pruritus associated with cholestasis in a

crossover trial involving 10 adults. They studied the acute effects of an intravenous injection of ondansetron (4 mg or 8 mg) or saline placebo in adults with cholestatic itch. The severity of itch was judged using an analog scale of 0 to 10. A successful treatment was considered an intensity reduction of ≥50% of itch within 2 hours of injection of the medication. Ondansetron reduced or abolished pruritus within 30 to 60 minutes after injection, and a 50% reduction of the itch intensity was observed for up to 6 hours following the injection of 8 mg.

However, the remaining literature concerning the efficacy of ondansetron remains contradictory.[27,28] In a prospective trial, 19 patients with resistant pruritus caused by cholestasis were randomized to receive ondansetron (8 mg) as an intravenous loading dose, followed by oral ondansetron (8 mg twice a day for 5 days), or placebo.[27] The degree of pruritus experienced was quantified using an hourly visual analog scale (VAS) and the amount of scratching was calculated using a piezo-electric crystal attached to the participants' fingernails. Although both the VAS and scratching activity decreased on the first day in both the ondansetron and the placebo groups, there was no difference between the two groups. The authors concluded that there was no benefit to short-term ondansetron treatment in this population. A subsequent randomized, double-blinded study attempted to determine the efficacy of ondansetron in relieving pruritus in 13 patients with chronic liver disease.[28] The participants were randomized to receive ondansetron (8 mg) or a placebo orally, administered three times a day for 4 weeks. The endpoints included a subjective score of pruritus and an objective measurement of 24-hour scratching activity. The subjective scale of pruritus included 0 (no pruritus) to 3 (severe pruritus with sleep deprivation and excoriations). Five patients in the ondansetron group had a clinically significant amelioration of the subjective perception of itching, although this did not correlate with a decrease in the amount of scratching. A systematic review performed by Timothy et al. evaluated five randomized, controlled studies on the efficacy of ondansetron on pruritus associated with either cholestasis or uremia.[29] Three of the five studies demonstrated a benefit from the use of ondansetron, but the effect was small and its clinical significance debatable.

CONCLUSIONS

In summary, we present anecdotal experience supporting the use of ondansetron to treat pruritus related to cholestasis in an adolescent following a prolonged course in the CTICU. The patient's pruritus had been recalcitrant to treatment with antihistamines, ursodeoxycholic acid, and the opioid antagonist naloxone. Although several case reports have suggested its efficacy in this clinical scenario, there remains a paucity of evidence-based medicine to clearly define its role. However, these studies are hampered by the subjective nature of pruritus, the significant potential for placebo effect, and the lack of objective measures of the severity of the problem or response to therapy. Although the amount of scratching observed is generally assumed to be an objective measure of itch, it may be impossible to differentiate how much is caused by actual itch versus an ingrained habit.

Clinical investigations demonstrate that serotonin plays a role as a mediator of itching and that increased serotonin activation of itch-sensitive nerve fibers causes pruritus in cholestasis. Thus, there appears to be a rational basis for the use of ondansetron in patients with cholestatic pruritus. Given its limited adverse effect profile, there are few concerns regarding its administration. We would speculate that the lack of consistent relief of itching found in randomized controlled trials could be due to ineffective dosing regimens (dose or interval) or the use of ondansetron as a monotherapy when a multidrug regimen would be more effective at alleviating pruritus. Perhaps, future trials should focus more on multidrug treatment given that there may be several mediators responsible for the difficult to treat and often refractory symptom, pruritus.

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ABBREVIATIONS 5-HT_3, 5-hydroxytryptamine; CTICU, cardiothoracic intensive care unit; ICU, intensive care unit; VAS, visual analog scale

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REFERENCES

1. Crowe J, Christensen E, Doniach D, et al. Early features of primary biliary cirrhosis: an analysis of 85 patients. *Am J Gastroenterol.* 1985;80(6):466-465.
2. Schoenfield LI, Christensen E, Doniach D, et al. Bile acids in the skin of patients with pruritic hepatobiliary disease. *Nature.* 1967;213(1):466-468.
3. Ghent CN, Bloomer JR, Klatskin G. Elevations in skin tissue levels of bile acids in human cholestasis: relation to serum levels and to pruritus. *Gastroenterology*. 1977;73(5):1125-1130.
4. Varadi DP. Pruritus induced by crude bile and purified bile acids. Experimental production of pruritus in human skin. *Arch Dermatol.* 1974;109(5):678-681.
5. Steinhoff M, Bienenstock J, Schmelz M, et al. Neurophysiological, neuroimmunological, and neuroendocrine basis of itch. *J Invest Derm.* 2006;126(8):1705-1718.
6. Greaves MW. Pathogenesis and treatment of pruritus. *Curr Allergy Asthma Rep*. 2010;10(4):236-242.
7. Yosipovitch G, Greaves MW, Schmelz M. Itch. *Lancet*. 2003;361(2):690-694.
8. Twycross R, Greaves MW, Handwerker H, et al. Itch: scratching more than the surface. *Q J Med.* 2003;96(1):7-26.
9. Glasova H, Beuers U. Extrahepatic manifestations of cholestasis. *J Gastro Hepat.* 2002;17(9):938-948.
10. Bergasa NV. The itch of liver disease. *Semin Cutan Med Surg.* 2011;30(2):93-98.
11. Zellos A, Roy A, Schwarz KB. Use of oral naltrexone for severe pruritus due to cholestatic liver disease in children. *J Pediatr Gastroenterol Nutr.* 2010;51(6):787-789.
12. Mansour-Ghanaei F, Taheri A, Froutan H, et al. Effect of oral naltrexone on pruritus in cholestatic patients. *World J Gastroenterol.* 2006;12(7):1125-1128.
13. Chang Y, Golkar L. The use of naltrexone in the management of severe generalized pruritus in biliary atresia: report of a case. *Pediatr Dermatol.* 2008;25(3):403-404.
14. Cies JJ, Giamalis JN. Treatment of cholestatic pruritus in children. *Am J Heath Syst Pharm*. 2007;64(11):1157-1162.
15. McRae CA, Prince MI, Hudson M, et al. Pain as a complication of use of opiate antagonists for symptom control in cholestasis. *Gastroenterology.* 2003;125(2):591-596.
16. Culy CR, Bhana N, Plosker GL. Ondansetron: a review of its use as an antiemetic in children. *Paediatr Drugs.* 2001;3(6):441-479.
17. Wilde MI, Markham A. Ondansetron: A review of its pharmacology and preliminary clinical findings in novel applications. *Drugs.* 1996;52(5):773-794.
18. Finn AL. Toxicity and side effects of ondansetron. *Semin Oncol.* 1992;19(suppl 10):53-60.
19. Layegh P, Mojahedi MJ, Malekshah PT, et al. Effect of oral granisetron in uremic pruritis. *Indian J Dermatol Venereol Leprol.* 2007;73(4):231-234.
20. Frigon C, Desparmet J. Ondansetron treatment in a child presenting with chronic intractable pruritis. *Pain Res Manag.* 2006;11(4):245-427.
21. Iatrou CA, Dragoumanis CK, Theodosia DV, et al. Prophylactic intravenous ondansetron and dolasetron in intrathecal morphine-induced pruritis: a randomized, double-blinded, placebo-controlled study. *Anesth Analg.* 2005;101(5):1516-1520.
22. Schwörer H, Ramadori G. Improvement of cholestatic pruritis by ondansetron. *Lancet.* 1993;341(5):1277-1278.
23. Di Martino M, Galanti B, Nardiello S. Treatment of cholestatic itching in primary biliary cirrhosis with ondansetron. *Ital J Gastroenterol.* 1995;27(8):455-456.
24. Trioche P, Samuel D, Odièvre M, et al. Ondansetron for pruritus in child with chronic cholestasis. *Eur J Pediatr.* 1996;155(11):990.
25. Raderer M, Müller C, Scheithauer W. Ondansetron for pruritus due to cholestasis. *N Engl J Med.* 1994;330(21):1540.

26. Schwörer H, Hartmann H, Ramadori G. Relief of cholestatic pruritis by a novel class of drugs: 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists: effectiveness of ondansetron. *Pain.* 1995;61(1):33-37.
27. O'Donohue JW, Pereira SP, Ashdown AC, et al. A controlled trial of ondansetron in the pruritis of cholestasis. *Ailment Pharmacol Ther.* 2005;21(8):1041-105.
28. Jones EA, Molenaar HA, Oosting J. Ondasetron and pruritis in chronic liver disease: a controlled study. *Hepatogastroenterology.* 2007;54(76):1196-1199.
29. Timothy HM, Clark K, Lam L, et al. The role of ondansetron in the management of cholestatic or uremic pruritus-A systematic review. *J Pain Symptom Manage*. 2012;44(5):725-730.