Ondansetron for Treating Itch in Healing Burns

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Abstract

Itching in healing burn wounds is a significant complaint in patients recovering from burn injuries. Current treatments for this itching are generally not as effective as would be desired. Antihistamines are commonly employed with some success but are far from completely satisfactory. Ondansetron has shown some effectiveness in treating pruritis from nonburn causes. This study is a double blinded, randomized, crossover trial comparing a single dose of 4mg Ondansetron to 25mg Dyphenhydramine for treating itch in healing burn wounds. 19 patients completed the study. 2 were withdrawn for protocol violations. In the remaining 17 patients Ondansetron was more effective than Dyphenhydramine in alleviating the itch (P<.05). While not completely effective, Ondansetron does offer another option in treating patients with pruritis from healing burns.

The Institution responsible for this paper is the US Army Institute of Surgical Research

BACKGROUND

A clear mechanism or cause for pruritus in patients recovering from burns has not been delineated. Pruritus is thought to be a sensory stimulus mediated by small peripheral afferent fibers stimulated and modulated by a host of mediators to include histamine, prostaglandins, interleukins, serotonin and centrally by inhibitory pathways[1]. Some studies have hypothesized that histamine or other granulation tissue could be responsible for pruritus. Antihistamines and other modes of peripherally inhibiting the sensation are used but no definitive treatment has been found[2,3].

While exact mechanisms/pathways for itching are currently unclear, histamine antagonism appears to be the most popular treatment. Whether histamine antagonism works predominately via peripheral inhibition or central sedation is uncertain. By treating another intermediary in the pruritus cascade, it may be possible that an alternate treatment could be used while eliminating some of the unwanted side effects of antihistamines. Although not evaluated in burn patients, serotonin inhibition has been used with some success to treat cholestatic itch, a dermatologic condition, and narcotic induced pruritus through an unknown mechanism[4,5,6,7].

Serotonin (5HT), a central and peripheral acting substance implicated in other pruritogenic processes such as uremia and cholestasis, could reasonably be implicated in the burn pruritus pathway as well[6]. Drawing from the same rationale that Schworer et al used for treating cholestatic pruritus with ondansetron, we hypothesize that ondansetron will be effective in treating pruritus in burn patients. Pain and itch are thought to be conducted via C-fibers that are influenced to a degree by serotonin (5HT). By inhibiting this influence at the 5HT3 receptor pruritus may also be inhibited.

Ondansetron is a 5HT3 receptor antagonist used for prevention of nausea and vomiting in patients receiving chemotherapy/radiation therapy. The drug has minimal side effects or drug-drug interactions, making it available to a wide patient population. Attempting to treat pruritus with serotonin antagonism could result in another tool for the treatment regimen, and possibly increasing efficacy over current standard of care

Other proposed ideas of peripherally inhibiting pruritus in burn patients include H1/H2 antagonism, massage therapy, eutectic mixture of local anesthetic (EMLA, Astra Pharma Inc.) crème, oatmeal paraffin baths and pulsed dye laser therapy with varying success, and no clearly effective solution[2,3,8,9] Histamine inhibition with H1/H2 blockers is by far the most popular modality of pruritus relief[10].

Aside from the histamine antagonism that is sedating, the rest of the therapies are time intensive and have limited

practical application for everyday use. The aforementioned treatments focus mainly on dealing with the problem peripherally. Studies involving intrathecal and parenteral narcotic induced pruritus demonstrated the potential of ondansetron to relieve pruritus both peripherally and centrally without the sedation side effects of antihistamines[4,9,11,12,13].

PATIENTS AND METHODS

This is a double - blinded randomized crossover design trial. The study was approved by our Institutional Review Board. Once the patients were identified with healing burn wounds that itch, met inclusion criteria and written informed consent was obtained, they were eligible for the study. Serving as their own control, patients were randomized between the test medication (ondansetron) and a control medication, which is the current standard of care antihistamine (diphenhydramine). The identity of the medications was blinded to all but the pharmacist. Patients were randomized to a group receiving either the test medication (ondansetron) first or a control medication (diphenhydramine) first on day 1. The opposite medication was given on day 2. The medications were labeled Study Drug #1 and Study Drug #2.

On day 1, when the patient experienced pruritus, he/she rated his/her pruritus intensity on a numeric analog scale from 0-10, where 0 equals “no itch” and 10 equals “the worst possible itch”. After rating the sensation the patient took Study Drug #1 (either 4 mg ondansetron or 25 mg diphenhydramine PO). Two hours after taking the medicine, the patient rated his/her pruritus score using the same intensity scale. On the second day (at least 24 hours post the first study drug administration), the patient was given Study Drug #2 orally. This medication was given at least 4 hours following the last dose of any standard therapy medication given. The pre-medication pruritus score and post medication pruritus score were recorded as with the first study medication. The patient documented the dates and times the medications was taken and the pruritus intensity score on the forms provided by the research staff. After taking the second study drug, the forms were mailed back to the research coordinator or taken back to the Burn clinic. Prior to enrollment, and following the study drug administration, the patient was permitted to receive the standard therapy for pruritus as rescue medication (diphenhydramine 25 mg every 4-6 hours as needed). Because a treatment exists for pruritus that has some proven benefit it was not seen as humane to allow patients to be subjected to a placebo controlled trial or to be left without rescue medication for a period to clear any medication in their systems that could confound the test drugs.

RESULTS

19 Patients completed the study. Two patients were excluded for protocol violations. One because he took the study drug when he wasn't itching and the other because he turned in results but there was no record that he actually picked up the study drugs.

Pretreatment itching scores were similar for both drugs 6.00 for dyphenhyrdamine and 6.35 for ondansetron. Post treatment scores were 3.41 for dyphenhydramine and 2.65 for ondansetron. The greater reduction in itch with ondansetron (3.70 vs 2.59) was statistically significant ($p<.05$)

DISCUSSION

Both drugs showed an improvement in symptoms. While the greater benefit in the ondansetron group was not dramatically better than dyphenhydramine any improvement is welcome with this difficult to treat problem.

There were a few barriers to an ideal situation to study ondansetron and diphenhydramine in this study. Patients involved with this study were all on an antihistamine prior to starting the study and during the study. It was not deemed ethical to allow a placebo controlled trial because it would mean that there was a possibility that standard of care was being withheld from the patients. Furthermore patients were allowed to take an antihistamine before and during the trial for breakthrough relief, because it was not deemed ethical to allow the patients to go without a rescue medication. Thus the results are confounded by the fact that antihistamines were used during the trial. With the information that ondansetron has shown some benefit, it is possible that a future study could randomize the patients to a longer course of a single drug and compare those results knowing that the drug the patient is taking is a pure representation of its effects.

Elucidating the true mechanism and pathophysiology of pruritus will help to strategically attack it, but until then specific alterations to this study will help. An extended course of ondansetron as opposed to a single dose will help exclude confounding drugs. A trial of varying doses of ondansetron will help identify a dose that could be efficacious. Testing of other serotonin receptor inhibitors may find an even more effective agent. Knowledge gained by performing these studies would possibly add another

medication to the arsenal for physicians looking to control pruritus that effects so many burn patients, and could offer an alternative to patients who find diphenhydramine either too sedating or ineffective.

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