Ondansetron for Treating Itch in Healing Burns
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Citation

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Ondansetron to 25mg Dyphenhydramine for treating itch in healing burn wounds. 19 patients completed the study. 2 were withdrawn for protocol violations.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.

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 pathways1. 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 found2,3.

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 mechanism4,5,6,7.

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 well8. 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 care9.

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 solution10. Histamine inhibition with H1/H2 blockers is by far the most popular modality of pruritus relief11.

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.\textsuperscript{4,9,11,12,13}

**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 dyphenhydramine 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 affects so many burn patients, and could offer an alternative to patients who find diphenhydramine either too sedating or ineffective.

References
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