

Title: Effect of long acting antihistamine on opioid- induced pruritus: A double-blind placebo controlled study

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NCT #: 01825655

Unique Protocol ID: HM20003779

Document approval date: August 26, 2015

Document Type: Protocol and SAP

## Protocol

### **Effect of long acting antihistamine on opioid- induced pruritus: A double-blind placebo controlled study.**

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## **Background and Significance:**

Opioids are commonly used in the treatment of moderate-severe pain. Pruritus is a common adverse effect of this class of medications, occurring in up to 10% of subjects treated with oral or intravenous opioids. [1]. The prevalence goes up with the dose of opioid being used [2]. The exact mechanism for the pruritus is unknown but there are two principal theories: A peripheral effect mediated by histamine released via direct mast cell degranulation by opioids; and a central mechanism mediated by  $\mu$  opioid receptors in the nervous system [3, 4].

Currently, there is no standardized treatment for opioid induced pruritus. Most studies conclude that opioid antagonists are the best treatment; however, they also decrease the analgesic effect. A recent study has compared Ondansetron and diphenhydramine treatment for pruritus in women who received intrathecal opioids and found them equally effective. [5]. This study was in adults receiving intrathecal opioid. There are no pediatric studies looking at effective treatment options for opioid-induced pruritus. As a consequence, the usual practice is to discontinue the opioid and use an alternate drug for analgesia. There are no prospective double blind studies available that have looked at the effect of a second-generation, non-sedating, long- acting antihistamine on opioid induced pruritus in children.

## **Hypothesis:**

Histamine is the primary mediator responsible for pruritus induced by oral or intravenous administration of opioids. A second generation, long acting antihistamine will be effective at relieving the pruritus and allowing continued therapy with opioids.

## **Specific aims:**

1. Our primary objective is to assess the efficacy of a long- acting antihistamine, Cetirizine, on opioid- induced pruritus in a double-blind, placebo controlled study. The primary outcome will be number of treatment failures between the treatment and placebo groups. Treatment failure is defined as persistent itch score of  $\geq 3$  3hrs after receiving the intervention.
2. Our secondary objectives are to analyze:
  - The correlation between baseline serum tryptase levels and the occurrence of opioid- induced pruritus.
  - The effect of age, race, sex on opioid induced pruritus and the influence of these parameters on antipruritic effect of the drug.

## **Methods:**

### **Subject recruitment:**

This study is a randomized, double blind placebo controlled study. Subjects 6-18yrs of age, requiring treatment with oral or intravenous opioids will be recruited from the pediatric inpatient units at Children's Hospital of Richmond at VCU.

### **Inclusion criteria:**

- Children age 6-18yrs on opioids who develop pruritus and are willing to participate in the study

### **Exclusion criterias:**

- Children with history of chronic urticaria
- Children with other chronic pruritic condition like eczema, contact dermatitis, psoriasis
- Children with known hypersensitivity to cetirizine/zyrtec
- Children on second generation antihistamine 1 week prior to the study recruitment
- Children who are unwilling or unable to swallow the capsule.
- Children with chronic liver or kidney disease

### **Study Design:**

After obtaining an informed consent from the parent or guardian, and an informed assent from children ages 12 years and above, serum tryptase levels will be drawn at baseline. For subjects whose baseline tryptase could not be drawn prior to the onset of itch symptom, a second attempt will be made either 24hrs after being symptom free or at a later date either in the inpatient or outpatient setting when they are free of symptoms.

Subjects who develop pruritus will have a baseline itch score measured at the onset of the itch symptom. Subjects with itch score of  $\geq 3$  will be randomized in a double blind fashion to the treatment group with cetirizine 10 mg once daily or to the placebo group. A tryptase level will be obtained 15-60 minutes after the onset of itching. Subjects will have itch scores measured at two time points from receiving the intervention, one at 3hours and other at 12 hours. Subjects will be allowed to receive rescue Diphenhydramine (Benadryl) 3 hours post intervention at the discretion of the treating physician.

Treatment failure is defined as an itch score of  $\geq 3$  at 3 hours post intervention and will result in discontinuation from the study. Successfully treated subjects will have a second itch score measured at 12 hours post intervention to analyze the persistence of antipruritic effect of the intervention. The numbers of treatment failures in each group are recorded. The total number of rescue Benadryl doses in each group will also be

recorded. The opioid dose, interval and total doses that each subject receives will be recorded. Patients whose treatment has been successful in controlling the pruritus (itch score  $\leq 2$ ) will continue in that arm for a maximum of 12 hours or till discharge whichever is earlier. Patients may drop out of the study at any time. The reason for dropping out will be recorded. At the conclusion of the study, patients will be reassessed by the primary team for further need for any anti-pruritic medications.

### **Primary Outcome**

Number of treatment failures in the study group versus the placebo group at 3 hours post randomization

### **Secondary Outcomes:**

1. Number of drop outs in the study group versus the placebo group at the end of the study period.
2. Tryptase levels (Total and mature) in subjects who develop opioid-induced pruritus versus those who do not.
3. Change in Tryptase levels (Total and mature) from baseline in subjects who develop pruritus
4. Effect of age, race, and sex on the incidence of opioid-induced pruritus
5. Effect of age, race, and sex on response to cetirizine in subjects with opioid-induced pruritus.
6. Change in the baseline itch score between treatment and the placebo group.
7. Number of rescue Benadryl doses between treatment and the placebo group.

### **Preliminary Results:**

Based on our experience (n=16) over the last few months, 37% (n=6) of patients treated with opioids in the inpatient setting develop pruritus. Of those 6 patients, 66.6% were successfully treated with an antihistamine and were able to continue treatment on the same opioid.

### **Statistical Method:**

Data will be analyzed using Chi square, student t-tests and Mann-Whitney U test (for non-parametric data) where appropriate. A p value of  $<0.05$  will be considered significant.

Assuming a 50% reduction in the failure rate to be clinically significant, a sample size of 66 confers a power of 0.8 at  $\alpha=0.05$ . Assuming a 10% drop out rate in each group a total of 73 patients will be recruited.

**Time line:**

We plan to recruit at least 1 patient per week for this study. The study should be completed in 2years. There is a real chance of completing this study much earlier than the 2 year time frame.

**Investigator responsibilities:**

- The study will be approved by the Western Institutional Review Board
- Conduct the study smoothly and effectively
- Report any adverse effects to McNeil Pharmaceuticals.
- At the completion of the study the data will be presented to McNeil before sending in for publication.

**Future research direction:**

1. To analyze the effect of antihistamine on opioid-induced itching in a much larger sample size.
2. To investigate titration prick skin testing to opioid as a predictor of opioid-induced itching.

**Limitation of the study:**

1. Itch scale is subjective and hence there is no objective way to assess improvement in itching

## Sample size calculation

Sample sizes for an  $\alpha = 0.05$  significance level with a two group continuity corrected  $\chi^2$  test of equal proportions – 1 sided test, equal sample sizes in each group

Placebo Group	Treatment Reduction	Treatment Group	Sample Size Per Group 80% Power	Sample Size Per Group 90% Power
0.3704	10% Reduction	0.3333	2,102	2,890
0.3922	15% Reduction	0.3333	857	1,174
0.4167	20% Reduction	0.3333	440	599
0.4444	25% Reduction	0.3333	255	346
0.4762	30% Reduction	0.3333	159	214
0.5556	40% Reduction	0.3333	70	90
<b>0.6667</b>	<b>50% Reduction</b>	<b>0.3333</b>	<b>33</b>	<b>43</b>
0.8333	60% Reduction	0.3333	15	19

## ITCH SCORE

	1=No pruritus	2=Mild pruritus (no intervention necessary)	3= Moderate pruritus (intervention necessary)	4= Severe pruritus
3hrs				
12hrs				

Description of the scores:

1. No pruritus- absence of any itching
2. Mild pruritus- presence of itching in only one location of the body (e.g. faces or arm). No intervention necessary as assessed by the investigator and the patient agreeing to the decision. Usually the itching is not relieved by the patient and only reported after being prompted by the investigator/
3. Moderate pruritus- presence of itching in more than one location, typical in 2 locations (e.g. arms and thorax). Intervention necessary as assessed by the investigator and the patient.
4. Severe pruritus- severe itching which involves almost the entire body and often disturbing the patient.

Score of  $\geq 3$ -included in the randomization

Improvement is a score of  $\leq 2$  at 3hrs



# References:

1. Reich A, Szepietowski JC. Opioid-induced pruritus: an update. *Clin Exp Dermatol*. 2010 Jan;35(1):2-6.
2. Bertz JM, Hermens JM, McMillan JC, Uno H, Hirshman C, Hanifin JM. Functional differences between human cutaneous mast cells and basophils: a comparison of morphine-induced histamine release. *Agents Actions*. 1986 Aug;18(5-6):455-62.
3. Fisher MM, Harle DG, Baldo BA. Anaphylactoid reactions to narcotic analgesics. *Clin Rev Allergy*. 1991 Fall-Winter;9(3-4):309-18.
4. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. *Am Fam Physician*. 2006 Oct 15;74(8):1347-54.
5. Siddik-Sayyid SM, Yazbeck-Karam VG, Zahreddine BW, Adham AM, Dagher CM, Saasouh WA, Aouad MT. Ondansetron is as effective as diphenhydramine for treatment of morphine-induced pruritus after cesarean delivery. *Acta Anaesthesiol Scand*. 2010 Jul;54(6):764-9.