Influence of Histamine Receptor Antagonists on the Outcome of Perforated Appendicitis

Analysis From a Prospective Trial

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Hypothesis: Diphenhydramine blocks the H_1 receptor to treat pruritus or to induce sleep, while ranitidine blocks the H_2 receptor to suppress gastric acid. They are often given to ill patients, such as those with perforated appendicitis. However, these receptors are integral to the inflammatory response, and to our knowledge, the impact of H_1 or H_2 blockade on outcome in the setting of perforated appendicitis has never been evaluated.

Design: Prospective randomized trial.

Setting: Referral center.

Patients: Children undergoing an operation for perforated appendicitis from April 2005 to November 2006.

Main Outcome Measures: We conducted multivariate analysis with Pearson correlation on data from a prospective randomized trial comparing antibiotic regimen after appendectomy for perforated appendicitis and outcome. Medications with a significant correlation to abscess development were investigated by comparing those receiving the medication with those who did not using the *t* test for continuous variables and χ^2 test for discrete variables. Significance was defined as $P \leq .05$.

Results: Significant correlations were found between the use of ranitidine ($P = .05$) or diphenhydramine ($P = .03$) and the development of an abscess. Direct comparison found no differences in patient or operative variables in those given either medication compared with those receiving no doses. Abscess rate in those receiving neither medication (n = 41) was 10%. Those given only ranitidine (n = 24) or diphenhydramine (n = 17) had doubled abscess rates of 17% and 18%, respectively. Those given both medications (n = 16) had a quadrupled abscess rate of 44% ($P = .03$).

Conclusions: Ranitidine or diphenhydramine given to patients with perforated appendicitis may increase the risk of postoperative abscess. Therefore, these medications should not be used empirically in this population.

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AFTER APPENDECTOMY FOR perforated appendicitis, patients usually require a few days to regain bowel function. During this period, they are normally allowed nothing by mouth or allowed insignificant intake like ice chips and sips of water. Most patients receive ketorolac tromethamine for pain, which can lead to gastritis, and narcotics, which can cause itching. These patients may be given a medication for gastric acid suppression or an antihistamine for itching or insomnia. In our hospital formulary, ranitidine is the medication available for gastric acid suppression and diphenhydramine is the antihistamine used for itching. Diphenhydramine exerts antihistamine effect by blocking the H_1 receptor on inflammatory cells, inhibiting the release of cytokine-rich granules from the cytoplasm.[1] This effect attenuates itching caused by narcotic-induced histamine release. Ranitidine is also a histamine antagonist, acting at the H_2 receptor to reduce acid production in the stomach by a noncholinergic pathway.[1] During the conduction of a prospective randomized trial on perforated appendicitis, we discovered that some patients were receiving ranitidine and the abscess rate appeared higher in these patients regardless of the antibiotic regimen. Therefore, at the end of this trial, we performed a thorough investigation of all medications given to these patients during the trial to elucidate the effect nonantimicrobial medications have on the outcome of patients with perforated appendicitis.

See Invited Critique at end of article

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METHODS

PATIENTS

After obtaining institutional board approval, a prospective randomized trial was conducted on children undergoing an operation for perfo-

Table 1. Demographics and Outcomes for H_1 Blockade

	Mean (SD)		
	Blocked (n = 33)	Not Blocked (n = 65)	*P* Value
Age, y	8.6 (4.5)	8.6 (4.2)	.97
Weight, kg	34.8 (23.1)	34.3 (20.9)	.96
Male, %	64	60	.79
Admission white blood cell count, /μL	0.0184 (0.0060)	0.0170 (0.0051)	.26
Days of symptoms at presentation	3.4 (2.7)	2.9 (1.7)	.26
Operation time, min:s	45:31 (24:35)	44:18 (20:54)	.80
Ranitidine use, %	48	37	.27
Ondansetron use, %[a]	82	88	.63
2-Antibiotic regimen, %	70	40	.001
Laparoscopy, %	100	97	.58
Abscess, %	30	12	.03
Wound infection, %	2	2	.99
Time to initial feeds, d	2.7 (2.1)	1.7 (1.0)	.004
Time to full feeds, d	3.9 (2.5)	2.8 (1.2)	.005
Hospital stay, d	7.9 (4.7)	5.6 (1.3)	.45

SI conversion factor: To convert white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a]Was given as ondansetron hydrochloride.

Table 2. Demographics and Outcomes for H_2 Blockade

	Mean (SD)		
	Blocked (n = 40)	Not Blocked (n = 58)	*P* Value
Age, y	8.7 (4.5)	8.5 (4.2)	.89
Weight, kg	34.3 (21.4)	34.5 (21.8)	.96
Male, %	63	59	.33
Admission white blood cell count, /μL	0.0170 (0.0055)	0.0179 (0.0054)	.46
Days of symptoms at presentation	3.1 (2.5)	3.0 (1.7)	.82
Operation time, min:s	43:03 (24:37)	45:51 (20:19)	.54
Diphenhydramine use, %	40	29	.25
Ondansetron use, %[a]	80	90	.29
2-Antibiotic regimen, %	50	50	.99
Laparoscopy, %	95	100	.16
Abscess, %	28	12	.047
Wound infection, %	0	2	.99
Time to initial feeds, d	2.2 (2.0)	2.0 (1.2)	.60
Time to full feeds, d	3.4 (2.3)	3.0 (1.3)	.30
Hospital stay, d	6.7 (3.2)	6.2 (3.0)	.45

SI conversion factor: To convert white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a]Was given as ondansetron hydrochloride.

rated appendicitis from April 2005 to November 2006.[2] Informed consent was obtained in all patients.

PROTOCOL

All patients with perforated appendicitis during this study received 5 days of intravenous antibiotics. Perforation was strictly defined as a hole in the appendix or a fecalith in the abdomen. On postoperative day 5, a white blood cell count was performed. If this was normal, patients were discharged home without antibiotics. If it was elevated, the patients received a minimum of 2 more days of intravenous antibiotics after which therapy was directed by the results of further studies. The antibiotic therapy was randomized to either standard triple therapy with ampicillin, gentamicin, and clindamycin or a 2-drug regimen of once-a-day dosing with ceftriaxone sodium and metronidazole.

The postoperative orders were computer entry from a standardized order set that listed the medications that could be chosen by simply checking the box next to each medication. Ranitidine was an option on the order set that was ordered in a provider-specific manner. The provider was not the surgeon in any case but was influenced by 4 surgical nurse practitioners or the rotating surgical residents. Diphenhydramine and ondansetron hydrochloride were both on the order set as options to order on an as-needed basis. Ketorolac could be ordered as a scheduled medication or an as-needed medication, and all patients received narcotics.

DATA COLLECTION

Demographics, admission data, hospital course, presence of medications, doses of medication, and all complications were analyzed from this prospective data set. A postoperative abscess was defined as an enhancing intra-abdominal fluid collection seen on computed tomographic scan obtained after postoperative day 5.

COMPARISONS

Multivariate analysis was performed to identify treatment variables that affected outcome. Pearson correlation was used to perform this analysis. The medications identified to independently hold a significantly positive correlation to abscess development were investigated directly with univariate analysis to assess for differences between those who received the medication and those who did not. The univariate comparison was done using the *t* test or χ^2 test to further delineate confounding variables. Significance was defined as $P \leq .05$. Descriptive statistics are listed as mean (SD).

RESULTS

In the multivariate analysis, there was no correlation between abscess and the administration of ketorolac, naloxone, or ondansetron. All patients received narcotics. Abscess rate was higher in patients who received either ranitidine ($P = .05$) or diphenhydramine ($P = .03$). Correlation of doses given and abscess rate was significant for ranitidine ($P = .003$), but not diphenhydramine ($P = .23$). There was no correlation between the presence of diphenhydramine and the presence of ranitidine. No differences existed in patient or operative variables in those given either medication compared with those receiving no doses.

Results of direct comparison by univariate analysis for patients who received diphenhydramine (H_1 blocked) compared with those who did not (H_1 unblocked) are displayed in **Table 1**. Results of direct comparison for patients who received ranitidine (H_2 blocked) compared with those who did not (H_2 unblocked) are displayed in **Table 2**.

Abscess rate in those receiving neither medication (n = 41) was 10%. Those given only ranitidine (n = 24) or diphenhydramine (n = 17) had doubled abscess rates of 17% and 18%, respectively. Those given both medications (n = 16) had a quadrupled abscess rate of 44% ($P = .03$).

COMMENT

Blockage of histamine receptors is ubiquitous in the practice of medicine. Diphenhydramine blocks the H_1 receptor and ranitidine blocks the H_2 receptor. These are both over-the-counter medications that are given by caregivers or taken by individuals without consideration of the importance of indication. H_1 blockade is usually administered with the intent of treating itching or allergies or simply inducing drowsiness. H_2 blockade is done with the intent of treating the vague and broad set of symptoms associated with gastritis or gastroesophageal reflux. However, the effect of blocking these receptors is diffusely integral to the inflammatory response, as both H_1 and H_2 receptors are expressed in vascular smooth muscle cells, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, dendritic cells, and T and B cells.[3] The clinical effects of blocking these pathways are not well described in the literature.

A prospective trial provides a means to gain insight on issues not directly addressed in the study design because of the prospective data set. In this example, we have a large data set of a homogenous population who reliably have had all necessary measurements to provide a valid analysis. More importantly, operative and postoperative management was controlled. The most concerning possible confounder in these findings would be the possibility that patients who were more ill and experienced a more difficult clinical course were more likely to receive the medications. If this were the case, the medications could simply represent a surrogate marker for progression toward abscess and do not possess a causative relationship. This is clearly not the case for ranitidine as we could trace the presence of the medication to the habits of a few nurse practitioners or rotating residents; administration was started within 24 hours in all cases, prior to any declaration of clinical course. Thus, the data on ranitidine represent a pseudorandomized study. The medications were identified as independent variables from the multivariate analysis. Subsequently, univariate comparisons to investigate equality in patient characteristics between those who were given ranitidine and those who were not was done to thoroughly investigate for patient differences that might be truly affecting outcome and leaving the medication as a surrogate measure of something. The results for ranitidine are outlined in Table 2 and show remarkable similarities in patient characteristics. A stronger argument might be made that diphenhydramine was given to patients requiring more narcotics and thus more likely to declare themselves as patients with an abscess. While this phenomenon may influence the data to an unknown degree, the impact of diphenhydramine on abscess cannot be entirely disregarded on these grounds. The clinical equality between those who were given diphenhydramine and those who were not is evident in Table 1. The only difference was the type of antibiotic regimen, which was not found to influence abscess development but seems more likely to indicate that the triple-antibiotic regimen is more likely to cause clinically detectable itching. Additionally, there is the lack of significant correlation between doses of diphenhydramine and doses of narcotics given prior to abscess detection ($P = .10$). Moreover, there was no correlation between abscess development and ketorolac or ondansetron use, both of which are more likely to be given in patients with more difficult early clinical courses. Finally, the additive effect of diphenhydramine and ranitidine is difficult to ignore or account for by any other explanation than that blockage of the histamine receptors has a negative impact on the peritoneal response and capacity for infection control. The possible mechanism for the observed outcomes deserves elaboration.

The local cellular immune response to an infectious source requires that immune cells identify the offending site via endothelial signaling and gain access to the tissue or space via an increase in endothelial permeability. H_1 receptor activation mediates endothelial signaling through increased expression of intracellular adhesion molecule 1, vascular cellular adhesion molecule 1, and P-selectin.[4-6] H_1 activation also promotes self-expression of the H_1 receptor, propagating the local response.[7]

The differentiation of monocytes into macrophages and dendritic cells after tissue migration is, in part, a histamine-mediated response involving both H_1 and H_2 receptors.[8] There is an upregulation of H_1 receptors associated with a reciprocal downregulation of H_2 receptors when monocytes differentiate into macrophages and an upregulation of H_1 receptors without change in the H_2 receptor population when monocytes differentiate into dendritic cells.[8] The resultant population of H_1 receptors on macrophages is functionally relevant as H_1 blockade has been shown to decrease monocyte-derived macrophage release of interleukin 8 (IL-8) and human lung macrophage release of IL-6.[9] H_1 antagonism has also been shown to downregulate the potent inflammatory transcription factor nuclear factor κB, with consequent suppression of local accumulation of inflammatory cells and the release of inflammatory cytokines.[10-12]

The antagonism of H_1 receptors results in a potent and multifaceted attenuation of the local immune response that may explain the phenomenon witnessed in this data set. The effect of antagonism of H_2 receptors is less clear given that the H_2 receptor mediates largely suppressive immunomodulatory events.[13-15] However, studies in receptor-null mice have demonstrated that H_2 receptor–deficient mice have decreased T-cell proliferation and downregulation of IL-2.[16] Two confounding factors exist in most studies evaluating histamine-mediated effects. One is that external application of histamine may interfere with endogenous histamine release and the other is that both H_1 and H_2 receptors exist simultaneously in immune cell systems. These factors may lead to confusing results. Therefore, the knockout model effectively confirms that mitogen-dependent T-cell proliferation is regulated by histamine through the H_2 receptor. This effect may contribute to the adverse impact on outcome for patients with intraperitoneal infection seen in patients treated with ranitidine in this study. However, the mechanism to account for the impact on outcome of both H_1 and H_2 antagonism is more complex and likely to become clearer as these receptors are studied further.

These data represent the first clinical evidence, to our knowledge, that both H_1 and H_2 receptor antagonism may

adversely affect postoperative abscess formation in patients with perforated appendicitis. While this is a novel concept for H_1 receptor antagonism, it is not for H_2 receptor antagonism. A large-scale population study in adults found a 1.63-fold increased risk of community-acquired pneumonia in patients using H_2 receptor antagonists.[17] Similarly, gastric acid suppression was found to increase the risk of community-acquired pneumonia in children as well, although only half of the suppressed patients were administered H_2 antagonists.[18] Many have held the philosophy that these findings are due to the acid suppression itself through the mechanism of increasing upper gastrointestinal tract bacterial flora, making previously subclinical aspiration become symptomatic. Our data suggest that perhaps H_2 antagonism may suppress important immune responses. Supporting this pathway with clinically convincing data are the results from a prospective trial in adults comparing ranitidine with sucralfate for stress ulcer prophylaxis, where O'Keefe et al[19] demonstrated an increase in overall infectious complications in the ranitidine group ($P = .001$). This effect persisted after catheter-related infections and secondary bacteremic events were excluded.

The data herein bolster the literature suggesting that H_2 receptor antagonism attenuates endogenous infection control pathways; in addition, our data suggest a novel observation that H_1 receptor antagonism is synergistic with H_2 antagonism. A prospective trial randomized on the use of these medications would be definitive, but at this point, we feel our data run contrary to the assumption of equipoise that is necessary for ethical enrollment into a clinical trial. We do not guarantee from this study design that these medications predictably double the risk of abscess, but we are confident that this information makes a strong argument that H_1 or H_2 blockade should not be routinely used without a clear indication.

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