

Histamine receptor antagonists and incident colorectal adenomas

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SUMMARY

Background: Prior studies suggest that histamines may modulate the development of colorectal neoplasia.

Aim: To assess whether histamine receptor antagonist use was associated with adenoma formation.

Methods: Patients ($n = 2366$) were drawn from three adenoma chemoprevention trials. All underwent baseline colonoscopy with removal of adenoma(s) and were deemed free of remaining lesions; they were followed with surveillance colonoscopy. Medication use was assessed by questionnaire. Adjusted risk ratios for adenoma formation related to histamine receptor antagonist use (histamine H1 and H2 receptor, H1RA and H2RA) were determined using log linear models.

Results: In pooled analyses, H1RA exposure was not associated with subsequent adenoma risk (RR = 1.10; 95% CI 0.97–1.25) or multiple adenoma formation (RR = 0.85; 95% CI 0.67–1.07). H2RA use also was not associated with adenoma (RR = 0.90; 95% CI 0.77–1.06), or multiple adenoma (RR = 0.77; 95% CI 0.57–1.04) in the pooled analyses, but H2RA users in the first trial had a decreased risk of adenoma (RR = 0.70; 95% CI 0.48–1.03) and multiple adenoma (RR = 0.31; 95% CI 0.12–0.79).

Conclusion: H2RA use was associated with reduced risk for adenoma in one trial, but not in the pooled analyses. Further study would be warranted before undertaking randomized trials of H2RAs for adenoma chemoprevention.

INTRODUCTION

Histamine is a biological amine that is widely distributed in mammalian tissues. Its effects are mediated through interactions with specific cell membrane receptors that have been characterized into four different subtypes (H1, H2, H3 and H4). Pharmacological agents that

block the H1 and H2 receptor have important clinical applications and are widely prescribed. Specifically, H1 receptor antagonists (H1RAs) downregulate the immune response and are prescribed for conditions such as allergic rhinitis^{1, 2} and H2 receptor antagonists (H2RAs) decrease acid secretion and are used in conditions such as gastro-oesophageal reflux disease (GERD).³

While the role of histamine in the immune cascade and acid suppression pathways is well recognized, it also has other biological effects. For example, histamine is a

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growth factor for certain colorectal cancer cell lines both *in vivo* and *in vitro*; these effects can be antagonized by the H2RA cimetidine.⁴ In a recent study cimetidine and ranitidine inhibited growth of the Caco-2 colorectal cancer cell line, and apoptosis was induced by both drugs.⁵ In a rat model of colon carcinogenesis, the H1RA chlorpheniramine maleate significantly inhibited aberrant crypt formation.⁶ In humans with colorectal cancer, H2RAs have been studied as adjuvant therapy with some suggestion of effectiveness.⁷⁻⁹

Colorectal adenomas are well-recognized precursors of colorectal cancer in humans. To date, there have been no formal studies examining the effect of H1RAs and H2RAs on adenoma development. Therefore, we examined the use of these drugs and their effect on incident adenomas in three large randomized chemoprevention trials.

METHODS

Subjects for this analysis were drawn from three randomized adenoma prevention trials: the Antioxidant Polyp Prevention Study,¹⁰ the Calcium Polyp Prevention Study¹¹ and the Aspirin/Folate Polyp Prevention Study.¹² Eligibility requirements for the three trials were similar. Patients qualified for the study by having at least one histologically documented colorectal adenoma removed shortly before study entry. Each had undergone a complete (i.e. to the caecum) colonoscopic 'clearing' examination within 3 months of study enrolment, with the endoscopist attesting that the mucosa was adequately visualized and that no known colorectal polyps remained. Patients were excluded if they had familial polyposis, invasive colorectal cancer, malabsorption syndromes, conditions that might be worsened by the study agents, or disorders treated by them.

At baseline, current medication use was gathered from the subjects via a questionnaire. After randomization, subjects routinely (every 4 or 6 months depending on the study) completed follow-up questionnaires that similarly ascertained medication use. All surveys requested information regarding both prescription and non-prescription medication use. Dosing information was not obtained.

Adenoma development after the clearing examination was assessed by subsequent surveillance colonoscopy. These examinations were routinely performed at both 1 and 4 years after baseline in the first two trials (antioxidant and calcium studies), and 3 years after baseline in the most recent (aspirin/folate) trial. The

location and size of all polyps removed from the bowel were noted, and tissue specimens were sent for central histopathology review.

Analysis

For our main analysis, subjects were considered to be H1RA or H2RA users if the database indicated usage at 'any' time during the study (baseline or follow-up questionnaire). As a crude assessment of dose, we further subdivided subjects based upon their recorded exposure to H1RAs and H2RAs. 'Low' usage was defined as subjects with 20% or fewer questionnaires indicating usage and 'high' usage was defined as >20% of questionnaires indicating usage.

To assure prospective analysis of exposure and outcome, adenoma development was assessed only on the basis of the final surveillance colonoscopy, i.e. the year 4 examination in the first two trials and the year 3 examination in the aspirin trial. We excluded from the analysis subjects not providing any data regarding medication use. To avoid misclassification of adenoma status, we also excluded those with 'interim examinations', which we defined as colonoscopy performed for clinical indications between year 1 and year 4 in the first two trials and between baseline and year 3 in the third trial.

In addition to examining our main outcome (any adenoma), we also examined the association of use of H1RAs and H2RAs with the risk of advanced adenomas and multiple adenomas. Advanced adenomas were defined as those ≥ 1 cm, >25% villous histology, high-grade dysplasia or cancer. Subjects were considered to have developed multiple adenomas if they had two or more adenomas at final (i.e. year 3 or year 4) colonoscopy.

Risk ratios were obtained by log-linear models and were adjusted for age, sex, clinical centre, treatment category, lifetime number of adenomas and duration of the observation period. A pooled estimate combining the results from all three studies was obtained by simple weighted averages of the study-specific estimates. Associations between histamine antagonist use and outcome are also reported for each individual study.

RESULTS

A total of 2915 subjects were randomized into the three parent trials. Of those, 2366 (81%) of those individuals

who had final colonoscopy (without interim examination) and provided complete data on medication usage form the cohort for this analysis. Subjects in the three studies were generally similar in age and ethnicity (Table 1). Efforts to enhance recruitment of females in the later studies resulted in a gradual increase in the number of women participating across the three trials. There was a marked increase in H1RA usage from <20% of subjects in the first two studies to 43% of subjects in the most recent aspirin/folate trial. Likewise, the overall frequency of reported H1RA use increased from 436 total reports of use in the first study to 1277 in the last (Figure 1). In contrast, there was a decrease in H2RA usage from 14.6% of subjects reporting any use in the antioxidant trial to 9.9% of subjects in the aspirin trial. Likewise, the overall frequency of reported H2RA use decreased from 396 total reports of use in the first study to 266 in the last (Figure 2).

In the pooled analysis, H1RA exposure was not associated with a reduction in subsequent development of adenomas (RR = 1.10; 95% CI 0.97–1.25) (Table 2). Likewise, there was no association between H1RA use and risk of advanced adenomas (RR = 1.13; 95% CI 0.83–1.54) or multiple adenomas (pooled RR = 0.85; 95% CI 0.67–1.07). There was no association between more frequent use of H1RAs and adenoma formation. Results from the individual trials did not indicate any clear association between H1RA use and adenoma risk (Table 2).

In the pooled analysis from the three trials there was no association between use of H2RAs and adenoma (RR = 0.90; 95% CI 0.77–1.06), advanced adenoma (RR = 1.15; 95% CI 0.80–1.65) or multiple adenoma (RR = 0.77; 95% CI 0.57–1.04) (Table 3). When the

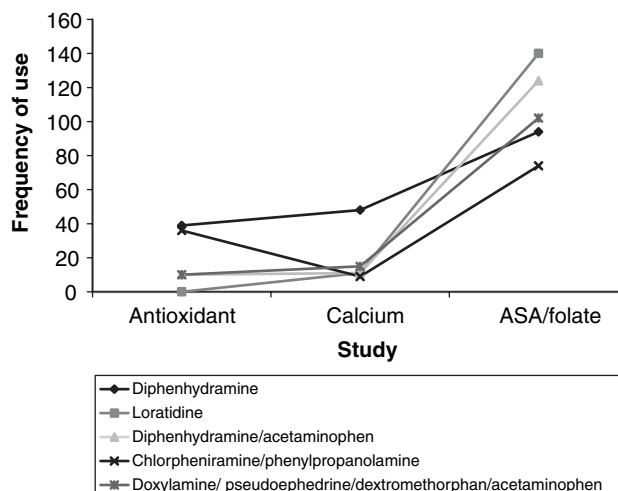


Figure 1. Total frequency of reported use (considering all questionnaires) of the five most commonly used H1RAs by study ($n = 650$).

trials were considered individually, there was a decreased risk of adenoma among H2RA users in the antioxidant trial (RR = 0.70; 95% CI 0.48–1.03) especially in those reporting more frequent use (RR = 0.54; 95% CI 0.31–0.94). Users of H2RAs in the antioxidant trial were also less likely to develop multiple adenomas (RR = 0.31; 95% CI 0.12–0.79). However, there was no clear indication of an association between H2RA use and adenoma in either the calcium trial or the aspirin/folate trial (Table 3).

DISCUSSION

We examined the effect of H1RA and H2RA usage on adenoma development in three large randomized con-

Table 1. Subject characteristics

	Antioxidant (1985–92)	Calcium (1989–97)	Aspirin/folate (1994–2001)
Study size (n)	605	741	1020
Age (mean \pm SD)	60.7 \pm 8.2	60.5 \pm 9.0	57.3 \pm 9.6
Sex (% male)	78.0	71.0	63.3
Race (%)			
Non-Hispanic white	85.1	85.6	85.9
Non-Hispanic black	7.1	7.8	5.3
Median follow-up time (months; mean \pm SD)	36.5 \pm 2.5	36.7 \pm 3.2	32.6 \pm 3.4
Adenoma recurrence (%)	33.2	32.1	42.6
Any advanced adenoma (%)	7.6	8.8	9.5
Multiple adenomas (%)	12.2	12.7	18.8
Any H1RA use after randomization (%)	18.4	13.8	43.1
Any H2RA use after randomization (%)	14.6	20.5	9.9

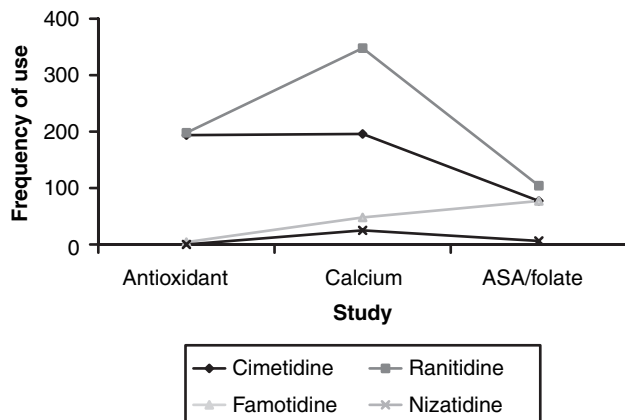


Figure 2. Total frequency of reported use (considering all questionnaires) of the four H2RAs by study ($n = 396$).

trolled trials of adenoma chemoprevention. In the pooled analysis, neither class of agent had a statistically significant association with subsequent adenoma formation.

Histamine is synthesized from L-histidine exclusively by the enzyme histidine decarboxylase and exerts its effects through four recognized receptors. The H1 receptor and H2 receptor are widely expressed in human tissues including epithelial cells and mediate their effects by way of G proteins to intracellular second messenger systems.¹³ Only the H1 and H2 receptor antagonists currently have any clinical application; there are over 40 H1RAs and four H2RAs available for clinical use.

We examined the association between H2RAs and adenoma formation because it has been proposed that

Table 2. Association between use of H1RA and risk of recurrent adenomas

	Antioxidant	Calcium	Aspirin/folate	Pooled
Any adenoma				
Any use after randomization	1.08 (0.80–1.45)	1.21 (0.90–1.64)	1.09 (0.93–1.26)	1.10 (0.97–1.25)
Infrequent ($\leq 20\%$)	0.92 (0.60–1.41)	1.09 (0.71–1.67)	1.12 (0.93–1.34)	1.07 (0.92–1.26)
Frequent ($>20\%$)	1.24 (0.85–1.81)	1.34 (0.90–1.99)	1.05 (0.87–1.27)	1.13 (0.96–1.32)
Any advanced adenoma				
Any use after randomization	0.71 (0.31–1.66)	1.49 (0.82–2.73)	1.13 (0.76–1.68)	1.13 (0.83–1.54)
Infrequent ($\leq 20\%$)	0.69 (0.22–2.17)	1.72 (0.81–3.65)	1.13 (0.70–1.83)	1.18 (0.81–1.73)
Frequent ($>20\%$)	0.75 (0.24–2.35)	1.26 (0.52–3.04)	1.12 (0.68–1.87)	1.07 (0.71–1.61)
Multiple adenomas (≥ 2)				
Any use after randomization	0.74 (0.39–1.41)	1.14 (0.64–2.03)	0.80 (0.60–1.05)	0.85 (0.67–1.07)
Infrequent ($\leq 20\%$)	0.69 (0.29–1.67)	1.26 (0.61–2.61)	0.75 (0.52–1.07)	0.81 (0.60–1.09)
Frequent ($>20\%$)	0.79 (0.33–1.90)	1.01 (0.43–2.37)	0.85 (0.60–1.20)	0.89 (0.66–1.20)

Values in RR (95% CI).

Table 3. Association between use of H2RAs and risk of recurrent adenomas

	Antioxidant	Calcium	Aspirin/folate	Pooled
Any adenoma				
Any use after randomization	0.70 (0.48–1.03)	0.95 (0.72–1.24)	0.99 (0.77–1.25)	0.90 (0.77–1.06)
Infrequent ($\leq 20\%$)	0.89 (0.56–1.44)	0.74 (0.46–1.19)	1.04 (0.75–1.44)	0.92 (0.73–1.16)
Frequent ($>20\%$)	0.54 (0.31–0.94)	1.07 (0.78–1.46)	0.93 (0.66–1.31)	0.88 (0.72–1.09)
Any advanced adenoma				
Any use after randomization	1.23 (0.56–2.69)	1.24 (0.71–2.16)	0.94 (0.48–1.81)	1.15 (0.80–1.65)
Infrequent ($\leq 20\%$)	0.97 (0.29–3.20)	0.68 (0.23–2.01)	1.28 (0.58–2.85)	1.06 (0.61–1.83)
Frequent ($>20\%$)	1.46 (0.57–3.74)	1.61 (0.86–3.03)	0.61 (0.20–1.84)	1.21 (0.77–1.91)
Multiple adenomas (≥ 2)				
Any use after randomization	0.31 (0.12–0.79)	0.66 (0.38–1.16)	1.09 (0.72–1.65)	0.77 (0.57–1.04)
Infrequent ($\leq 20\%$)	0.24 (0.05–1.09)	0.23 (0.05–0.94)	1.24 (0.73–2.12)	0.71 (0.45–1.11)
Frequent ($>20\%$)	0.36 (0.12–1.12)	0.95 (0.50–1.83)	0.94 (0.51–1.73)	0.81 (0.56–1.20)

Values in RR (95% CI).

Statistically significant values are highlighted in bold.

these agents might reduce colorectal carcinogenesis via downregulation of signal transduction pathways that promote cell growth. Histamine can stimulate both cyclic monophosphate and inositol triphosphate signalling cascades.¹⁴ Furthermore, activation of the human H2 receptor in stable transfected cancer cell lines leads to the induction of the *c-fos* oncogene with an increase in cellular proliferation.¹⁵ With respect to colorectal carcinogenesis, Adams et al.⁴ examined the effect of histamine on the colonic adenocarcinoma cell line C170. In that study, histamine stimulated a dose-dependent increase in cAMP that was antagonized by the H2RA cimetidine.

While our pooled result from the three trials does not indicate an antineoplastic effect for use of either H1RAs or H2RAs, an association between H2RA use and adenoma development was suggested in the antioxidant trial, the earliest of our three studies. While the play of chance cannot be dismissed as a basis for the differences in results among trials, it is interesting to note that there were important differences among the trials. For example, in the latter two trials in which H2RAs had no effect, the study interventions (calcium and aspirin) were themselves effective. The effectiveness of these agents might have made it more difficult to discern a small benefit afforded by H2RA use. Also, the patterns of H2RA use among participants in the three studies changed over time. Clearly, the introduction of proton pump inhibitors and their superiority in blocking gastric acid relative to H2RAs has changed the management of conditions associated with excess gastric acid.¹⁶ It is likely that H2RA use was much more on an 'as needed' basis (e.g. 'breakthrough therapy' in GERD) in the later studies when proton pump inhibitors were widely available for daily symptom control. Lower dose 'over the counter' use was also introduced during this time frame,^{17, 18} which again might diminish our ability to observe an effect, if one existed. Our assessment of exposure does not allow us to distinguish between daily or 'as needed' use nor does it allow us to distinguish over-the-counter use vs. prescription use and thus we cannot examine these ideas directly.

We did not find a reduction in adenoma recurrence with the use of H1RA. Similar to their H2 receptor counterparts, experimental stimulation of H1 receptors has also been associated with cellular proliferation. For example, histamine acts as a growth factor in HeLa and in human epidermal carcinoma cells A431, activating cellular proliferation in those expressing functional H1

receptors.¹⁹ There are fewer pre-clinical studies looking specifically at H1 signalling and colorectal carcinogenesis. In one study, 78 potential chemopreventive agents were evaluated in a rat model assessing how well the various agents inhibited carcinogen-induced aberrant crypt foci (ACF) in the colon.⁶ The H1RAs, including chlorpheniramine maleate, meclizine and triprolidine were all very effective suppressors of ACF. Clearly, our findings are not consistent with these results. Unlike the study in rats, we did examine both sedating and non-sedating antihistamines in our analysis. However, our findings were generally consistent over time (i.e. even prior to widespread prescribing of non-sedating antihistamines) so this is unlikely to explain the discrepancy.

The strengths of this study include the large pool of subjects available for analysis, the assessment of drug use by a standard survey that included questions about both prescription and over-the-counter use, and the prospective and standardized ascertainment of adenomas. Moreover, a single-study pathologist confirmed the histopathological diagnoses of all adenomas identified during the study. Finally, the assessment of both exposure and outcome was consistent across the three trials.

The major limitation of our study is that we did not have specific information on frequency of use, duration of use or dosage for the drugs that were studied. To assess dose response we utilized the frequency of reported use (i.e. >20% of surveys) as a surrogate for actual dosage information. Also, while our total subject population from the three studies was large there was only limited numbers of our secondary end points (multiple polyps and advanced polyps), and thus our analyses had limited statistical power for these outcomes.

In our pooled analyses, neither exposure to H1RAs nor H2RAs had a significant effect on adenoma occurrence. The trend towards reduction in adenoma recurrence in users of H2RAs in our antioxidant trial is provocative, but was not confirmed in later investigations. Further research on the effects of exposure to H2RAs and adenoma risk is recommended before proceeding with a randomized controlled trial of this agent for chemoprevention of colorectal neoplasms.

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