Effect of Histamine-2 Receptor Antagonists on Blood Alcohol Levels

A Meta-Analysis

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OBJECTIVE: To determine the effect, if any, of histamine type 2 receptor antagonists (H_2 RAs) on serum alcohol levels under various conditions including type of H_2 RA receptor antagonist, alcohol dose, and fed status of the subject.

STUDY DESIGN: Meta-analysis of the published literature.

DATA SOURCES: Studies were identified by MEDLINE (January 1982 through December 1997) using the key words H_2 receptor antagonists and alcohol. Other studies were identified by reviewing bibliographies of retrieved articles and by discussion with colleagues.

STUDY SELECTION: Studies were selected if they involved the coadministration of H_2 RAs and alcohol in healthy, human volunteers. Studies that may have addressed this goal but were performed in another context, for instance the measurement of ulcer healing, were excluded.

DATA EXTRACTION: Data were extracted on the design, number of participants, participant characteristics, type and dose of H_2 RA administered, serum alcohol levels (measured as C_{max}) along with standard deviations, dose of alcohol received, and fed or fasted status of participants. Alcohol dose was arbitrarily divided into low dose (≤ 0.5 g/kg body weight) versus high dose (> 0.5 g/kg body weight). In addition, studies involving ranitidine and cimetidine were stratified by sample size into small ($n \leq 10$) versus not small ($n > 10$).

MEASUREMENTS AND MAIN RESULTS: Twenty-four trials met selection criteria. Small elevations in C_{max} were noted when cimetidine (2.71 mg/DL; 95% confidence interval [CI] 1.60, 3.83) or ranitidine (6.95 mg/DL; 95% CI 5.83, 8.08) were coadministered with alcohol. No such differences were noted for famotidine (0.28 mg/DL; 95% CI -1.24, 1.80) or nizatidine (2.33 mg/DL; 95% CI -0.06, 4.72). The elevation detected with cimetidine and ranitidine was most pronounced in smaller studies ($n < 10$). Separate analyses investigating the effect of alcohol dose and fed or fasted status of participants revealed no clinically important differences.

CONCLUSIONS: Cimetidine and ranitidine, but not the other H_2 RAs, can cause small elevations of serum alcohol level when alcohol and drug are administered concurrently. Studies with larger numbers of participants were less likely to

demonstrate this effect. Relative to accepted, legal definitions of intoxication, the effect of any H_2 RA on blood alcohol level is unlikely to be clinically relevant.

KEY WORDS: H_2 receptor antagonists; blood alcohol level; meta-analysis.

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Histamine type 2 receptor antagonists (H_2 RAs) are among the most prescribed drugs in the world. Use of these agents has further increased with the recent availability of low-dose, over-the-counter preparations. For the most part, these drugs are remarkably safe. However, concern has been raised about their effect on serum alcohol levels. Early studies suggested that cimetidine, ranitidine, and nizatidine, but not famotidine, increased blood ethanol levels in volunteers when administered concurrently with alcohol.¹⁻⁴ Subsequent studies have reached conflicting results.⁵ Many of these reports have been criticized regarding issues of study design including small sample sizes, heterogeneity of study populations, amount and timing of alcohol ingestion, and the fed or fasted status of participants.⁶

Social consumption of alcohol is extremely common. Increased access to H_2 RAs through nonprescription sales further elevates the likelihood of concomitant intake. If co-ingestion were to increase peak serum alcohol levels above the standard legal definition of intoxication or, equally importantly, to impair psychomotor function substantially more than alcohol alone, it would carry important medical and legal implications for both prescribing physicians and pharmaceutical companies.

In an effort to resolve the question of an important interaction, we performed a meta-analysis of the available literature pertaining to H_2 RAs and blood ethanol levels in humans.

Methods

Literature Search

Clinical trials that compared the effect of H_2 RA ingestion on serum alcohol levels in healthy, human volunteers were identified through MEDLINE search of articles published from January 1982 through December 1997 using the key words H_2 receptor antagonists and alcohol. Other articles were identified through a manual review of the references of potentially relevant articles and from discussions with colleagues. Studies performed in the context of other clinical questions or conditions, such as the effect of H_2 RA on peptic ulcer,⁷ in patients undergoing endoscopy,⁸ or the role of variations in first-pass metabolism or

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genetic polymorphisms,^{9,10} were excluded. Articles were also excluded from analysis if trials were reported in abstract form only or were preliminary publications for which more mature data were subsequently presented.

Data Extraction

All data were extracted by reviewers aware of the study hypotheses. Data were collected onto standardized forms by two reviewers (DSW and JAB) for each article. These results were compared for agreement. In the event of a discrepancy, the article was rereviewed to reach a consensus. From the reported trials we identified the numbers of patients in each H₂RA treatment or control group. Maximum serum alcohol levels ($C_{\max}$) with and without alcohol ingestion were recorded for each, as were fed or fasted status and alcohol dose. Alcohol dose was arbitrarily grouped into low dose (≤ 0.5 g/kg body weight) or high dose (> 0.5 g/kg body weight). The H₂RA doses were recorded. Studies involving cimetidine and ranitidine were also classified by sample size, as small ($n \leq 10$) or large ($n > 10$). Trials of the other two H₂RA agents were insufficient in number to permit this stratification.

Statistical Analysis

We used methods for combining continuous outcomes across studies recommended by Follmann et al.¹¹ The general approach involves computing a weighted average of the within-study differences in the mean $C_{\max}$ between the treated (H₂RA) and untreated (no H₂RA) conditions. The approach we used involved weighting by the sample size for each study and assumes a common change variance for all studies. The common change variance (the variance of the difference of observations between treated and untreated conditions) was estimated from all studies that reported either an actual change variance or a p value that could be used to back calculate a t statistic and a corresponding change variance. The average change variance was derived from 17 comparisons reported in 11 studies.^{2,3,12-20}

Two other choices of weights described by Follmann et al.¹¹ gave similar results, so only the results using sample size weights are presented.

In addition to performing formal tests of heterogeneity, which are known to lack adequate statistical power,²¹ we made an a priori decision to explore potential sources of heterogeneity directly. Specifically, we calculated separate summaries of studies with fed subjects versus those with fasted subjects, and low-dose studies (defined as ethanol at 0.5 g/kg of body weight or lower) versus high-dose studies (more than 0.5 g/kg). For famotidine, there was only one study of fasting subjects.²² For nizatidine, the small number of studies (only three), did not permit stratification.

To investigate the possibility of publication bias, i.e., the differential reporting of studies based on statistical significance, we generated plots of the mean difference in $C_{\max}$ within a study versus the sample size, separately for

cimetidine and ranitidine. This is commonly known as a funnel plot. In the absence of publication bias, the plotted points should appear to form an inverted funnel shape, with high variability for studies with small sample sizes and lower variability for large studies, but with all points "centered" around the (presumed) true value. When there appears to be a "bite" removed from the funnel (e.g., there is an absence of small studies showing no effect or an effect in a negative direction), that is considered to provide evidence of publication bias.²³ Because the plot of the cimetidine studies revealed evidence of publication bias, we chose an arbitrary threshold of a sample size of more than 10, and calculated separate summaries for cimetidine and ranitidine, in which only these "large" studies were included.

RESULTS

Twenty-nine trials published between January 1982 and December 1997 compared serum alcohol levels in subjects who were also administered a variety of H₂RAs. Four were considered ineligible for review for the reasons described above.⁷⁻¹⁰ Twenty-four trials were eligible for this meta-analysis.^{1-6,12-20,24-30} Several studies administered more than one drug. These trials are listed in Table 1.

Total daily study doses for the various H₂RAs were as follows: cimetidine, 400–1200 mg; ranitidine, 300 mg; famotidine, 40 mg; and nizatidine, 200–300 mg. The effects were similar across the dose ranges for cimetidine and nizatidine. Therefore results for all doses are reported together.

As noted, all but one of the trials used a crossover design. One trial randomized subjects to two of four regimens.⁶ It was not possible to discern the composition of each treatment group, leaving open the possibility of substantial overlap of treated subjects versus control subjects. For the purposes of this analysis, it was also treated as a crossover trial.

Overall, the mean differences in $C_{\max}$ between treated subjects and untreated subjects for the different H₂RAs are displayed in Table 2. When all studies are considered, administration of cimetidine (mean 2.71; 95% confidence interval [CI] 1.60, 3.83) and ranitidine (mean 6.95; 95% CI 5.83, 8.08) resulted in small but significantly higher serum alcohol levels than in control subjects. In many fewer studies, nizatidine administration (mean 2.33; 95% CI –0.06, 4.72) showed a trend toward significance, while famotidine administration resulted in no effect (mean 0.28; 95% CI –1.24, 1.80). In a series of sensitivity analyses, the effect of ranitidine was greatly reduced after the removal of one study,²⁹ which employed a much higher alcohol dose than all others (1.6 vs 0.8 g/kg body weight in the studies with the next-highest alcohol dose).

Table 2 also shows the effects of fed or fasted status on serum alcohol level and H₂RA intake. This analysis does not include one study,²⁵ because the fed or fasted status was not described. Regardless of food intake, cimetidine and ranitidine resulted in modestly higher serum

Table 1. Summary of Studies Included for Analysis

Study Reference	H ₂ RA*	Subjects, n	Fed/Fasted	Ethanol Dose, g/kg
Burnham et al. ¹⁹	F	24	Fed	0.15
Caballeria et al. ¹	C	6	Fed	0.15
Clemmesen et al. ³⁰	C	12	Fasted	0.15 or 0.45
Dauncey et al. ²⁸	C,R	10	Fasted	0.5
DiPadova et al. ²	C,R,F	6	Fed	0.3
Dobrilla et al. ²⁴	C,R	6	Fed	0.8
Feeley & Wood ¹²	C	6	Fasted	0.8
Fraser et al. ⁶	C,R,F	12	Fed	0.3
Fraser et al. ⁴	C,R,F	23	Fed	0.8
Fraser et al. ¹⁸	R	20	Fed	0.3
Guram et al. ³	C,R,F,N	6	Fed	0.75
Hernandez-Munoz et al. ¹⁴	C,F	5	Fed	0.15
Jonsson et al. ²⁷	C,R	12	Fasted	0.8
Kendall et al. ²⁰	C,R,F	24	Fed	0.5–0.8
Mallat et al. ¹⁵	C,R,F	12	Fed	0.3
Palmer et al. ¹⁷	C	23	Fed	0.15
Palmer et al. ¹⁷	C,R,N	23	Fed	0.15
Papke et al. ²⁶	C	10	Fasted	0.8
Raufman et al. ⁵	C,R,F,N	23	Fed	0.3
Seitz et al. ¹³	C,R	8	Fed	0.8
Sharma et al. ¹⁶	C	11	Fed	0.3
Tanaka & Nakamura ²²	C,R,F	6	Fasted	0.8
Toon et al. ²⁹	R	18	Fed/Fasted	0.5
Webster et al. ²⁵	C,R	7	Not	0.7

*C indicates cimetidine; R, ranitidine; F, famotidine; N, nizatidine.

Table 2. Summary of Studies by Agent, Study Size, Fed Status, and Alcohol Dose

Study Drug	Total Studies, n	Total Subjects, n	Mean Δ, mg/DL	Standard Error, mg/DL	95% CI, mg/DL
Cimetidine					
All	24	263	2.71	0.57	1.60, 3.83
Fed	14	198	2.44	0.67	1.12, 3.76
Fasted	9	68	1.69	1.12	−0.50, 3.88
Low EtOH	14	155	1.56	0.74	0.11, 3.01
High EtOH	10	108	4.37	0.89	2.63, 6.11
n > 10	9	163	0.12	0.72	−1.29, 1.54
Ranitidine					
All	18	257	6.95	0.57	5.83, 8.08
Minus outliers	16	221	1.98	0.62	0.76, 3.20
Fed	13	208	3.25	0.64	1.99, 4.50
Fed minus outlier	12	190	1.19	0.67	−0.13, 2.50
Fasted	4	42	21.14	1.42	18.35, 23.93
Fasted minus outlier	3	24	−0.50	1.88	−4.19, 3.19
Low EtOH	8	128	2.15	0.81	0.55, 3.74
High EtOH	10	129	11.73	0.81	10.13, 13.32
High EtOH minus outlier	8	93	1.75	0.96	−0.13, 3.62
n > 10	11	210	7.53	0.64	6.08, 8.57
n > 10 minus outliers	9	174	1.08	0.69	−0.29, 2.45
Famotidine					
All	10	141	0.28	0.78	−1.24, 1.80
Fed	9	135	0.20	0.79	−1.35, 1.76
Low EtOH	6	82	0.18	1.02	−1.82, 2.18
High EtOH	4	59	0.42	1.20	−1.94, 2.77
Nizatidine					
All	3	48	2.33	1.22	−0.06, 4.72

alcohol levels, while famotidine had no effect. There were too few studies with nizatidine for comparison.

The effects of low doses versus high doses of alcohol on serum alcohol levels are displayed in Table 2. Higher alcohol loads resulted in slightly higher absolute differences when H₂RAs were coingested. The result, however, was not clinically significant compared with blood levels satisfying the legal definition of alcohol intoxication. When various combinations of fed or fasted status and low dose or high dose of alcohol were considered, there were no substantial differences (data not shown).

The effect of sample size is important in comparing the effects of the various H₂RAs. This variation is displayed graphically as a funnel plot (Fig. 1) for studies of cimetidine. When these reports are stratified by sample size, the effect of coadministration of ethanol is substantially tempered. Specifically, in studies of cimetidine with sample sizes greater than 10, the difference in C_{max} for subjects exposed to alcohol was only 0.12 (95% CI, -1.29, 1.54), while the pooled difference for all studies of cimetidine was 2.71. These results suggest the presence of publication bias for studies of cimetidine. Such a pattern was not as pronounced for studies of ranitidine.

DISCUSSION

Each of the H₂RAs appears on a recent list of the most frequently prescribed medications in the United States.³¹ When over-the-counter preparations are also considered, it is reasonable to assume that coingestion of alcohol and H₂RAs occurs frequently. If alcohol levels were substantially increased, or psychomotor function impaired by these medications, then coadministration would pose a concern to patients and physicians.

Ethanol is absorbed in the upper gastrointestinal tract and metabolized nearly entirely in the liver.³² There is evidence that some portion of ingested alcohol does not enter the systemic circulation.³³ Gastric mucosa possesses alcohol dehydrogenase (ADH), an enzyme required for alcohol metabolism.³⁴ The recognition that some H₂RAs were able to inhibit gastric ADH in vitro initiated concerns about the

interaction between these medications and alcohol. The extent of any important biological relation is unclear. The liver possesses a greater capacity to metabolize alcohol than the stomach.³⁵ There may, in fact, be insufficient amounts of gastric ADH to break down even small amounts of alcohol (0.3 g/kg body weight).³⁶

Although there is disagreement about the mechanism of alcohol metabolism, there is no argument about its substantial public health effects. Nearly three quarters of the U.S. population consumes alcohol. It is estimated that up to 10% of the population meet criteria for alcohol dependence or abuse.³⁷ Prior to the introduction of the over-the-counter versions, H₂RAs generated over \$5 billion in annual sales. If some or all of the H₂RAs increase alcohol levels or impair psychomotor function, it might be reasonable to suggest that other classes of acid-suppression drugs like proton pump inhibitors be substituted, as there is no evidence these agents affect serum alcohol concentrations.²⁷ Conversely, the absence of substantive interaction would free physicians or pharmaceutical companies from any liability related to the concomitant ingestion of alcohol and the medications prescribed or produced. Previous studies have not documented any substantial difference in psychomotor function between subjects consuming set alcohol doses and those consuming the same alcohol dose plus H₂RAs.^{38,39} Neither ranitidine nor nizatidine had any effect on a variety of measures. Although the other H₂RAs have not been studied, it is reasonable to assume similar results.

We endeavored to define review criteria and apply them equally to each study before including it in our analysis. Although it is possible to overcome the type II error that may plague individual studies, meta-analysis cannot correct biases or suboptimal design strategies in the original reports: for example, the inclusion of undetected alcoholics who might have depressed gastric ADH levels,³⁴ the effect of including study subjects of different ethnic backgrounds who may have genetically different abilities to metabolize equivalent amounts of alcohol,⁴⁰ or women who may have lower levels of gastric ADH.³⁵ Finally, it is important to recognize that presumably healthy subjects were the participants in the studies pooled for analysis. The effects of H₂RA use on serum alcohol levels of persons with different disease states cannot be assessed.

As mentioned, we stratified a priori, on the basis of alcohol dose and fed or fasting status, factors we believed to be the key experimental features of the various studies. When formal testing was performed, heterogeneity among studies overall was high (data not shown). However, little heterogeneity was found among those studies of cimetidine or ranitidine with more than 10 subjects, and among any studies with famotidine or nizatidine. While we cannot rule out subgroups in which coingestion of H₂RAs and alcohol may have greater effects, the overall impact is small.

It is further recognized that C_{max} may not be an optimal end point. It is dependent on numerous factors including the volume of distribution of alcohol and the

FIGURE 1. Funnel plot of sample size versus mean C_{max}.

timing of sample collection. However, peak alcohol levels are of some legal significance. Comparisons of area under the curve distributions may be preferable, but this value was not reported in many studies, nor could it be reliably back-calculated from available information. Recognizing these inherent limitations, a meta-analysis can bring together sufficient data to answer questions with more confidence.

Overall, the mean difference between treated and untreated individuals ranged from 0.28 mg/DL for famotidine to 6.95 mg/DL for ranitidine. Legal intoxication in most states is defined as a blood ethanol level ≥ 100 mg/DL. The contribution of H₂RA ingestion is trivial in comparison with the absolute value, although concurrent ingestion could occasionally increase the ethanol level above that defining intoxication. Importantly, some prior concerns about the interaction of specific H₂RAs and high doses versus low doses of alcohol, or fed versus fasted state seem unfounded. Because meta-analysis includes patients from a variety of clinical settings and study designs, results may be more generalizable than those from a single study.

Finally, it is worth noting that the reports most likely to detect a difference in $C_{\max}$ were those with the smallest sample sizes. When the evidence is displayed graphically (see Fig. 1), publication bias is apparent. Specifically, these findings suggest the preferential publication of small studies only when large effects are observed. Some of the continuing controversy over H₂RAs and alcohol may stem from the publication of series with small numbers of subjects.

In summary, there is little evidence to suggest that any of the H₂RAs has a meaningful effect on blood alcohol levels. This holds true regardless of medication, amount of alcohol ingested, and fed status of the study subjects. Although concomitant alcohol and H₂RA intake led to a higher $C_{\max}$, relative to standard legal definitions of intoxication, the elevations are unlikely to be clinically relevant.

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