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H₂ antihistamines for the treatment of anaphylaxis with and without shock: a systematic review

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ABSTRACT

Background: Anaphylaxis is a serious allergic or hypersensitivity reaction, which is rapid in onset and sometimes can prove fatal. Although H₂ antihistamines are often administered for emergency treatment in anaphylaxis, there is uncertainty about their effectiveness in this disease.

Objective: To assess the benefits and harms of H₂ antihistamines in the treatment of anaphylaxis.

Methods: A systematic review was performed of randomized controlled trials and quasi-randomized controlled trials comparing H₂ antihistamines with placebo or no intervention in patients with anaphylaxis.

Results: The authors failed to identify any eligible studies for inclusion in this systematic review.

Conclusions: When H₂ antihistamines are recommended for anaphylaxis treatment, the status of the evidence base supporting their use should be described. Well-designed randomized controlled trials investigating the role of H₂ antihistamines in anaphylaxis treatment are urgently needed.

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Introduction

Anaphylaxis is a serious allergic or hypersensitivity reaction with a sudden onset (minutes to a few hours after exposure to the inciting agent) and a potentially fatal outcome.^{1,2} The initial pharmacologic intervention of choice is epinephrine (adrenaline) (R.L. Campbell et al, unpublished data, 2013).^{1–8} Anaphylaxis guidelines describe H₂ antihistamines as “second-line”^{2–7} (R.L. Campbell et al, unpublished data, 2013) or even “third-line”⁸ medications and advise administering them concurrently with an H₁ antihistamine. Nevertheless, H₂ antihistamines are widely available for anaphylaxis treatment⁹ and are commonly administered for the initial treatment of anaphylaxis;^{10,11} indeed, in some hospital emergency departments, these ancillary or adjunctive medications are given more frequently than epinephrine.^{10,11}

Several anaphylaxis guidelines specifically recommend ranitidine in a dose of 1 mg/kg (dose 50–150 mg in adults and 12.5–50 mg in children) given by intravenous infusion over 10 to 15 minutes.^{4,5} Cimetidine and famotidine are also used. Doses are extrapolated from the use of H₂ antihistamines for treatment of peptic ulcer disease and prophylaxis against stress ulcers in high-risk patients in critical care units.¹² Sometimes only a single

H₂ antihistamine dose is administered; at most, only a few doses are given.

The authors previously published a Cochrane review of H₁ antihistamines in the treatment of anaphylaxis in which they found no randomized or quasi-randomized trials for or against their use.¹³ They noted that H₁ antihistamine dose regimens in anaphylaxis are extrapolated from those used in urticaria treatment; in addition, only symptoms of itching, flushing, urticaria, and rhinorrhea are relieved, and onset of action is slow.

In the present study, the authors review the action of histamine at H₂ receptors in the pathophysiology of anaphylaxis, provide the rationale for a systematic review of H₂ antihistamines in the treatment of anaphylaxis, and report the findings from their review.

Histamine in Anaphylaxis

Histamine, administered by intravenous infusion to healthy adults, can reproduce the symptoms of anaphylaxis.¹⁴ It leads to increased vascular permeability and vascular smooth muscle relaxation, followed by vasodilation, potential decrease of circulating blood volume, hypotension, and distributive shock. In the upper airway, it contributes to laryngeal edema, and in the lower airways, it contributes to smooth muscle contraction. In the gastrointestinal tract, histamine-induced smooth muscle contraction, plasma extravasation, and glandular secretion can lead to crampy abdominal pain, vomiting, and diarrhea.¹⁴

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Many of the pathophysiologic events in anaphylaxis attributed to histamine occur through histamine H₁ receptors; however, some symptoms, such as flushing, headache, and hypotension owing to vasodilation, occur through H₁ receptors and H₂ receptors.^{14,15}

Pretreatment with an H₁ antihistamine and an H₂ antihistamine concurrently before histamine infusion is more effective than pretreatment with an H₁ antihistamine alone or an H₂ antihistamine alone for decreasing the elevated heart rate, widened pulse pressure, cutaneous flush, and pulsatile headache produced by histamine infusion.^{14,16}

H₂ Receptors and H₂ Antihistamines

H₂ receptors have been comprehensively studied. The gene encoding the human H₂ receptor has been cloned. The mechanism of action of H₂ antihistamines as inverse agonists at H₂ receptors was described in 1996; subsequent to this discovery, these medications have optimally been described as H₂ antihistamines, not as H₂ blockers or H₂ antagonists.^{17–21}

H₂ receptors are widely distributed throughout the body. Through inverse agonism at H₂ receptors on the acid-secreting parietal cells in the gastric mucosa, H₂ antihistamines suppress basal gastric secretions. Through inverse agonism at H₂ receptors on vascular smooth muscle cells, myocardial cells, and other cells, they decrease vascular permeability, hypotension, flushing, headache, and tachycardia. They also decrease mucous production, especially in the airways.^{19–22}

Four H₂ antihistamines with chemical structures homologous to histamine, cimetidine and the more potent ranitidine, famotidine, and nizatidine, are widely used, primarily for inhibition of gastric acid secretion and treatment or prophylaxis of peptic ulcer disease and uncomplicated gastroesophageal reflux.^{12,22} Among allergic diseases, they are used only for the treatment of urticaria²³ and anaphylaxis.^{10,11} Although many novel H₂ antihistamines have been developed, owing to class issues including species specificity, high potential for drug–drug interactions, and toxicity, only a few of these novel H₂ antihistamines, such as roxatidine, oxmetidine, lafutidine, and ebrotidine, have been studied in humans,²⁴ and these medications have not gained regulatory approval in most countries.

Clinical Pharmacology of H₂ Antihistamines

After intravenous dosing, the principal route of administration generally used in anaphylaxis, therapeutic H₂ antihistamine levels are achieved rapidly and maintained for up to 5 hours after cimetidine, 8 hours after ranitidine, and 12 hours after famotidine. H₂ antihistamine elimination is principally through renal excretion of unchanged drug, with 10% to 35% undergoing hepatic metabolism. H₂ antihistamines cross the placenta and are excreted in breast milk.²²

Short-term H₂ antihistamine treatment is well tolerated in most patients. After rapid intravenous infusion of cimetidine or ranitidine, hypotension has been reported. After intravenous dosing in the elderly, central nervous system effects, such as confusion, delirium, hallucinations, slurred speech, and headache, can occur;²² however, this does not appear to be a contraindication to their use in elderly patients with anaphylaxis.²⁵ Potential minor, transient, reversible effects, such as diarrhea, headache, drowsiness, fatigue, and muscular pain, are uncommon. Neuroendocrine effects, blood dyscrasias, and hepatic toxicity are highly unlikely after only a few doses.²²

Although H₂ antihistamines appear to be safe for short-term use in anaphylaxis, the evidence base for their effectiveness and safety in this life-threatening disease has not been systematically reviewed.

Methods

The authors systematically searched for randomized and quasi-randomized controlled trials of H₂ antihistamines in anaphylaxis. They searched the Cochrane Central Register of Controlled Trials (CENTRAL) to June 2013 (Appendix 1), the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects (DARE) to June 2013 (Appendix 1), MEDLINE (Ovid SP, 1966 to May 2013; Appendix 2), EMBASE (OVID SP, 1966 to May 2013; Appendix 3), CINAHL (EBSCO host, 1982 to May 2013; Appendix 4), ISI Web of Science (1945 to May 2013; Appendix 5), and TRIP database (www.tripdatabase.com) to June 2013.

No language or geographic restrictions were imposed. To find relevant unpublished or on-going studies, the authors searched 3 international trial repositories: <http://www.clinicaltrials.gov>, <http://www.controlled-trials.com>, and <http://www.anzctr.org.au>. In addition, they searched the bibliographies of identified studies.

Eligibility Criteria for Considering Studies for This Systematic Review

Types of studies

The authors planned to include studies with higher forms of evidence, ie, randomized controlled trials and quasi-randomized controlled trials comparing H₂ antihistamines with placebo or no intervention in patients with anaphylaxis.

Types of participants

The authors were interested in all patients (ie, infants, children, and adults), managed in any setting (ie, community and hospital/medical), experiencing anaphylaxis caused by any trigger (including food, medication, insect or reptile venom, exercise), regardless of the severity of the episode, the risk status of the patient, and patient comorbidities.

Types of intervention

The authors considered studies in which H₂ antihistamines were administered by the oral, intramuscular, or intravenous route to treat an acute episode of anaphylaxis, regardless of whether the treatment was given by a medical professional or patient or caregiver. They specifically chose to exclude studies in which H₂ antihistamines were used prophylactically to prevent anaphylaxis. In the search strategy, they used the following terms to identify H₂ antihistamines: histamine H₂ antagonists, H₂ receptor antagonists, H₂ blockade, and H₂ receptor blockade; they also searched for specific H₂ antihistamines (Appendix 1).

Types of outcome measurements

The primary outcomes of interest were clinical improvement or resolution of symptoms as determined by an objective measurement and mortality rate. Secondary outcomes of interest included hospital admission rate; duration of hospital admission; hospital readmission rates; rates of protracted, biphasic, and delayed reactions; cost-effectiveness; and rates of iatrogenic adverse effects.

Data Collection, Quality Appraisal, and Analysis

Study selection

Two authors (U.B.N. and E.R.) independently reviewed the titles and abstracts generated by the literature searches with a view to selecting potentially eligible studies using the criteria delineated earlier. It was planned that disagreements would be resolved by discussion between the 2 authors with possible recourse to additional independent reviewers (A.S. and F.E.R.S.) if a consensus could not be reached; however, this was not necessary.

Data extraction

Two authors (U.B.N. and E.R.) would independently extract data into a preagreed standard data extraction form based on that used

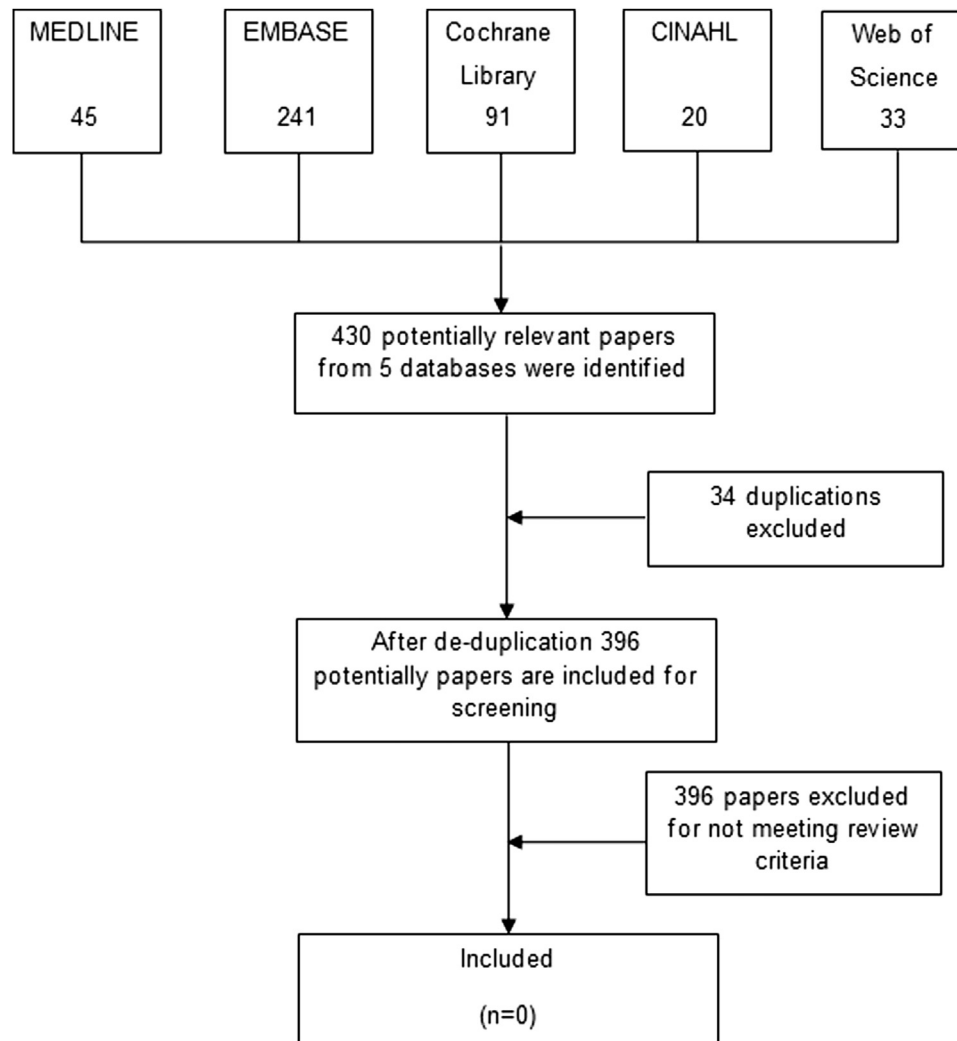


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

by the Cochrane Anaesthesia Review Group. Disagreements were to be resolved by discussion with the involvement of a third reviewer (A.S.), if necessary.

Assessment of methodologic quality of included studies

Critical appraisal of each included study was to be performed by 2 independent authors (U.B.N. and E.R.) using the methods detailed in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*.²⁶ The authors planned to focus on the following domains to assess the quality of studies: adequate sequence generation; allocation concealment; blinding (of subjects, researchers, outcome assessors, or data analysts); incomplete outcome data adequately addressed; free of selective reporting; and free of other bias. Each parameter would be given a judgment: “yes,” indicating low risk of bias; “no,” indicating high risk of bias; and “unclear,” indicating uncertain risk of bias. Then, taken together, an overall judgment of each article was to be made: ie, high, moderate, or low quality. When discrepancies existed between reviewers (E.R. and U.B.N.), attempts were to be made to achieve a consensus; if this was not possible, a third independent reviewer (A.S. or F.E.R.S.) was to be consulted.

Data Analysis and Synthesis

The authors planned to provide a descriptive summary of the data in narrative and tabular forms. Then, they intended to use

Review Manager (RevMan version 5.2; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for data analysis and quantitative data synthesis. For dichotomous data, they planned to calculate individual and pooled statistics as relative risks with 95% confidence intervals. For continuous data, they hoped to calculate individual and pooled statistics as mean differences and/or standardized means differences with 95% confidence intervals.

The authors planned to consider whether meta-analysis was appropriate in the presence of significant clinical or statistical heterogeneity. They planned to test for heterogeneity using the I^2 statistic. Significant heterogeneity would have been assumed at an I^2 value greater than 40% (ie, >40% of variability in outcome between trials could not be explained by sampling variation).²⁷ If able to pursue a meta-analysis, the authors would have used fixed-effect or random-effects modeling depending on whether the data were found to be homogenous. In the absence of any substantial statistical or clinical heterogeneity, they planned to report a fixed-model derived pooled effect. They intended to conduct, wherever possible, quantitative analyses of outcomes on an intention-to-treat basis. Then, they would have assessed evidence of publication bias graphically using funnel plots and statistically using Begg and Egger tests.^{28,29}

In the event of statistical or clinical heterogeneity, the authors had hoped to consider undertaking a subgroup analysis. The subgroups of interest would have been:

- Presence or absence of shock or respiratory compromise
- Mild or severe anaphylaxis³⁰
- H₂ antihistamine administered
- Mode of administration
- Time from onset of anaphylaxis to receipt of treatment
- Age of patient (infant, child, and adult)

The authors planned to perform a sensitivity analysis for the allocation of missing data by best- and worst-case analyses and a sensitivity analysis based on including only randomized studies to assess the impact on the review conclusions of excluding studies judged to be at high risk of bias.

Results

The searches yielded 430 potentially eligible studies (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram in Figure 1). The authors failed to identify any studies that met their eligibility criteria.

However, the authors found a small number of potentially relevant studies that were eventually excluded. In 1 double-blinded, placebo-controlled, randomized trial, participants with acute allergic syndromes were treated with an H₁ antihistamine (diphenhydramine 50 mg intravenously [IV]) and placebo or an H₁-antihistamine (diphenhydramine 50 mg IV) and an H₂ antihistamine (cimetidine 300 mg IV). Better outcomes, specifically improvement or resolution of cutaneous symptoms, were seen in the latter group.³¹ In a similar prospective, randomized, double-blinded study, patients with acute allergic reactions were treated with an H₁-antihistamine (diphenhydramine 50 mg IV) and placebo, an H₂ antihistamine (ranitidine 50 mg IV) and placebo, or an H₁-antihistamine (diphenhydramine 50 mg IV) and an H₂ antihistamine (ranitidine 50 mg IV). This trial showed that the combined H₁ and H₂ antihistamine treatment improved resolution of acute urticaria.³² Most patients enrolled in these 2 trials presented with cutaneous symptoms and signs (erythema, pruritus, urticaria, and/or angioedema); the minority had wheezing, stridor, abdominal symptoms, or hypotension.^{31,32} In a small randomized, single-blinded, crossover study, healthy volunteers received an infusion of histamine and saline or histamine and an H₁ antihistamine (dimethindene 4 mg IV) and an H₂ antihistamine (cimetidine 200 mg IV), and their blood pressure and heart rate were subsequently monitored.³³ In the 2 groups, the mean arterial pressure decreased and a tachycardia was noted, but these resolved in the treatment group, leading the authors to conclude that H₁- and H₂ antihistamines administered concurrently are effective in the treatment of histamine-induced cardiovascular reactions.

Discussion

Statement of Principal Findings

Despite an extensive and comprehensive literature search, the authors found no high-quality evidence in support of or against the use of H₂ antihistamines in the emergency management of anaphylaxis as currently defined.²

Strengths and Limitations of This Review

The key strengths of this review relate to the use of established systematic review methods, the comprehensiveness of the searches without any language restrictions, the range of outcomes of interest, and the established methods through which the authors planned to critically evaluate the quality of the trial evidence.

The main limitations of this review are those common to systematic reviews in general. This includes the possibility that the authors may have failed to identify some published studies or work in progress; however, they believe this to be unlikely.

Implications for Clinical Practice and Future Research

Because the authors were unable to find any relevant evidence for the use of H₂ antihistamines in the treatment of anaphylaxis, they are unable to make any definitive recommendations for or against their use in clinical practice. However, based on the clear recommendations from available evidence-based guidelines, they can underscore the importance of epinephrine being used as the first-line agent and emphasize that H₂ antihistamines should not be administered ahead of, or instead of, this potentially life-saving treatment (R.L. Campbell et al, unpublished data, 2013).^{1–8} In this respect, it is also important that future anaphylaxis guidelines recommending the use of H₂ antihistamines are clear about the status of the evidence base supporting this recommendation.³⁴ Some published anaphylaxis guidelines already include this information (R.L. Campbell et al, unpublished data, 2013).^{1–8}

Undertaking clinical trials in the context of anaphylaxis is inherently challenging, but it should be feasible for agents such as H₂ antihistamines and for H₁ antihistamines and glucocorticosteroids.^{35,36} Given that H₂ antihistamines are widely available and widely used in clinical practice, are safe for short-term use, and concealment of H₂ antihistamine use vs placebo or no intervention does not present any problem, a strong case can be made for undertaking such trials.³⁶ These would ideally be multicenter, placebo-controlled investigations conducted in patients with anaphylaxis who have been promptly assessed and treated with epinephrine, appropriate positioning, supplemental oxygen, and intravenous fluids^{3–7} before intervention with a second-line medication, such as an H₂ antihistamine, or placebo.³⁶ These trials will need to define and select appropriate target patients, use an appropriate comparator therapy, study the outcome measurements detailed earlier, including adverse effects and cost-effectiveness, include an a priori planned subgroup analysis along the lines indicated earlier, and be adequately powered to detect any differences in outcomes.

Appendix 1

Search Strategy for CENTRAL, the Cochrane Library

- #1 MeSH descriptor Anaphylaxis explode all trees
- #2 anaphyla*
- #3 anaphyla* near (shock* or syndrome* or react*)
- #4 anaphyla* and (shock* or syndrome* or react*)
- #5 acute systemic allergic react*
- #6 idiopathic anaphylaxis
- #7 systemic anaphylaxis
- #8 anaphylactoid*
- #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
- #10 MeSH descriptor Histamine H₂ Antagonists explode all trees
- #11 antihistamin*
- #12 (Cimetidine or Tagamet or Peptimax or Famotidine or Pepcid or pepcidtwo or Nizatidine or Axid or Ranitidine or Zantac or Gavilast or Gavilast-p or Histac or Pylorid or Ranitic or Ranitil or Ranzac or exp Histamine H₂ Antagonists or H₂ receptor antagonists or H₂ blockade or H₂ receptor blocker*)
- #13 (#10 OR #11 OR #12)
- #14 (#9 AND #13)

Appendix 2

Search Strategy for MEDLINE (Ovid SP)

- (Anaphylact\$ or anaphylax\$ or idiopathic or (acute adj5 allergic react\$)).mp. or exp ANAPHYLAXIS/
- (Cimetidine or Tagamet or Peptimax or Famotidine or Pepcid or pepcidtwo or Nizatidine or Axid or Ranitidine or Zantac or

Gavilast or Gavilast-p or Histac or Pylorid or Ranitic or Ranitil or Ranzac or exp Histamine H₂ Antagonists or H₂ receptor antagonists or H₂ blockade or H₂ receptor blocker*)

3. 1 and 2

4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

5. 3 and 4

Appendix 3

Search Strategy for EMBASE (Ovid SP)

1. (Anaphylact\$ or anaphylax\$ or idiopathic or (acute adj5 allergic react\$)).mp. or exp ANAPHYLAXIS/ or exp ANAPHYLACTIC SHOCK/

2. (Cimetidine or Tagamet or Peptimax or Famotidine or Pepcid or pepcidtwo or Nizatidine or Axid or Ranitidine or Zantac or Gavilast or Gavilast-p or Histac or Pylorid or Ranitic or Ranitil or Ranzac or exp Histamine H₂ Antagonists or H₂ receptor antagonists or H₂ blockade or H₂ receptor blocker*)

3. 1 and 2

4. (placebo.sh. or controlled study.ab. or random*.ti.ab. or trial*.ti.ab.) not (animals not (humans and animals)).sh.

5. 3 and 4

Appendix 4

Search Strategy for CINAHL (EBSCO Host)

S1 (MM "Anaphylaxis")

S2 TX Anaphylact* or anaphylax*

S3 AB acute and AB allergic react*

S4 S1 or S2 or S3

S5 (MM "Histamine H₂ Antagonists+")

S6 TX (Cimetidine or Tagamet or Peptimax or Famotidine or Pepcid or pepcidtwo or Nizatidine or Axid or Ranitidine or Zantac or Gavilast or Gavilast-p or Histac or Pylorid or Ranitic or Ranitil or Ranzac or exp Histamine H₂ Antagonists or H₂ receptor antagonists or H₂ blockade or H₂ receptor blocker*)

S7 S5 or S6

S8 S4 and S7

Appendix 5

Search Strategy for ISI Web of Science

#1 TS=(Anaphylact* or anaphylax*) or TS=(acute SAME (allergic react*))

#2 TS=((or Cimetidine or Tagamet or Peptimax or Famotidine or Pepcid or pepcidtwo or Nizatidine or Axid or Ranitidine or Zantac or Gavilast or Gavilast-p or Histac or Pylorid or Ranitic or Ranitil or Ranzac or Histamine H₂ Antagonists or H₂ receptor antagonists or H₂ blockade H₂ receptor blocker*))

#3 TS=(random* or placebo or multicenter or prospective) or TS=((controlled or clinical) SAME trial*) or TS=((single or double or triple or treble) SAME (mask* or blind*))

#4 #1 AND #2 AND #3

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