H2 The Rescue?

The Use of H2 Antagonists in Acute Allergic Reactions

Alexandra Newman
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Contents

Introduction

The topic is whether H_2 antagonists improve outcomes in patients with acute allergic reactions. Case reports and non-blinded studies in the 1980s first suggested this on the basis that histamine$_2$ receptors are involved in vasodilatation and capillary permeability.[1,2] Several studies have also looked at H_2 antagonists in chronic urticaria. It doesn't appear in the Resuscitation Council UK algorithm for treatment of anaphylaxis.[3]

Reason For Topic Choice

I started considering this after managing a patient severe allergic angioedema and airway obstruction. Adrenaline, chlorphenamine and hydrocortisone had been given and a cricothyroidotomy performed, however the patient still progressed to cardiac arrest and died. It was suggested we could have given ranitidine as it was also an antihistamine. I wondered if this could have made any difference.

Clinical Scenario

A 30 year old female presents to the Emergency Department with widespread urticaria and pruritis which started 3 hours previously after eating a seafood salad. She has had chlorphenamine and prednisolone but after 2 hours the symptoms have not settled. Could an H_2 antagonist help?

Three part question

In [and adult patient with acute allergic reaction of less than 72 hours duration] does a [H_2 antagonist] improve [resolution of symptoms]?

Search strategy

A search was conducted using the following databases and resources via the Athens system:

- AMED
- BNI
- CINAHL
- EMBASE
- MEDLINE

The search strategy is as follows:

[(Acute AND (Anaphyl* OR Allerg* OR angioedem* OR urticari*)) AND (H2 OR Ranitidine OR Famotidine OR Cimetidine OR Nizatidine OR (Histamine AND antagonist))] Limit to human and English.

Table 1 *Search results*

Database	Results
AMED	0
BNI	0
CINAHL	11
EMBASE	91
MEDLINE	72

Results were de-duplicated. Google, the Cochrane Library and references of relevant papers found were also searched. The search results were narrowed down by looking at the titles and abstracts, concentrating on Randomised Controlled Trials (RCTs) looking at clinical outcomes. Table 2 shows the papers identified that looked at H_1 and H_2 antagonists for acute allergic reactions.

Table 2 *Papers of Interest*

Title	Author	Journal	Year	Country	Patient Group	Study Type	Main Outcomes	Key Results	Study Limitations
Comparison of Cimetidine and Diphenhydramine in the Treatment of Acute Urticaria[4]	Moscati *et al.*	Annals of Emergency Medicine	1990	USA	93 ED patients age 14-56, urticaria <72 hours. Randomised to diphenhydramine 50mg IM (DPH group) vs cimetidine 300mg IM (CTD group). Exclusion: respiratory signs & symptoms, hypotension, pregnancy, allergy to study medication, concurrent antihistamine or steroid use, chronic respiratory cardiovascular, hepatic or renal disease.	Prospective double blind RCT	Relief of itch (patient rated scale 0-3) Relief of wheal intensity (physician rated scale 0-3) Sedation (patient rated scale 0-2) Relief of wheal extent (physician rated scale 1-3) Overall patient rated improvement (better, same or worse)	Both groups improved, no significant difference Both groups improved, no significant difference CTD group sedation 0.37 on scale compared to 1.085 DPH group, p=<0.0001 Both groups improved, no significant difference CTD group 87% improvement, DPH group 76% improvement – not significant	Small numbers Randomisation done by alternating patients Clinical outcome measure not validated IM route not widely used

| Histamine Antagonists in the Treatment of Acute Allergic Reactions[5] | Runge *et al* | Annals of Emergency Medicine | 1992 | USA | 39 ED patients age 18-50, pruritis, urticaria, throat tightness, facial swelling <12 hours. Randomised to diphenhydramine + placebo (DPH group) vs cimetidine + placebo (CTD group) vs diphenhydramine + cimetidine (DPH + CTD group). Exclusion: Concurrent antihistamine or steroid use, allergy to study drugs, heart disease, pregnancy or lactation, abnormal mental status, asthma, COPD, no telephone, experimental drug use, respiratory distress, unstable vital signs. | Prospective double blind RCT | Relief of pruritis(relief score difference between baseline 110mm VAS and 30 minute 110mm VAS, relief score >25mm considered clinically significant)

Relief of urticaria (relief score difference between baseline 110mm VAS and 30 minute 110mm VAS, relief score >25mm considered clinically significant) | 35 patients. DPH group mean relief score 80.3, CTD 48.8, DPH + CTD 68.5 (p=0.022). Clinically significant relief 12/12 DPH group (p=0.029) compared to 6/10 CTD, no significant difference for DPH + CTD 12/13 patients

33 patients. No significant difference between groups for relief scores but 11/12 DPH + CTD patients significant relief compared to 8/10 CTD and 5/11 DPH (p=0.027) | Small numbers

Randomisation not fully explained

Significantly less urticaria in DPN group |
|---|---|---|---|---|---|---|---|---|---|

Improved Outcomes in Patients With Acute Allergic Syndromes Who Are Treated With Combined H_1 and H_2 Antagonists[6]	Lin *et al*	Annals of Emergency Medicine	2000	USA	91 ED patients age >18, urticaria, pruritis, angioedema, stridor <12 hours. Randomised to diphenhydramine 50mg + placebo IV (DPH group) vs diphenhydramine 50mg + ranitidine 50mg IV (RAT group). Physician rated outcomes at 0, 60 and 120 minutes. Exclusion: Pregnancy.	Prospective double blind RCT	Resolution of urticaria	53 patients. 91.7% patients in RAT group relief of symptoms. 73.8% in DPH group. P=0.2	Convenience sample of 100 Patients enrolled when study physicians available
							Resolution of angioedema	No significant difference between groups. Both showed improvement	
							Resolution of urticaria and angioedema in patients with either or both symptoms	72 patients. 70.5% patients improved RAT group, 46.5% DPH group p=0.02 Multivariate analysis OR 2.8 in favour RAT p=0.048	
Famotidine in the treatment of acute urticaria[7]	Watson *et al*	Clinical and Experimental Dermatology	2000	USA	25 ED patients age 18-55, urticaria <72 hours. Randomised to famotidine 20mg IM vs diphenhydramine 50mg IM. Patients	Prospective double blind RCT	Intensity of urticaria (100mm VAS doctor assessed)	No significant difference between groups. Both showed significant improvement	Very small sample size Unclear method of randomisation

					rated symptoms on VAS at 0 and 30 minutes. Exclusions: Allergy to study medications, pregnancy or lactating, bronchospasm, pharyngeal oedema, haemodynamic instability, angioedema, unable to understand questionnaire or consent.		Sedation (100mm VAS patient assessed)	Non-significant increase in sedation with diphenhydramine	IM route of administration not used often
							% body surface area urticaria (rule of 9s doctor assessed)	No significant difference between groups but trend towards famotidine	
							Relief of pruritis (100mm VAS patient assessed)	No significant difference between groups but trend towards diphenhydramine	

Moscati *et al*

This randomised prospective double-blind clinical trial compares cimetidine and diphenhydramine for treatment of acute urticaria. Primary outcomes were intensity and distribution of urticaria, degree of pruritis and sedation.

Patients aged 14 and 56 years old presenting to the Emergency Department of an American Army Hospital over 4 months with acute urticaria (wheals and diffuse itching < 72 hours duration) were included. Exclusion criteria were respiratory symptoms or signs, hypotension, pregnancy, allergy to study medication, current use of antihistamines or steroids, history of chronic respiratory, cardiovascular, renal or hepatic disease.

The Emergency Medicine physician initially rated wheal intensity on a numeric scale (0-3), and distribution on a body chart. Patients rated degree of pruritis and sedation on the scale.

Patients were allocated either cimetidine 300mg or diphenhydramine 50mg intra-muscularly according to their enrolment number being odd or even by a nurse who also administered the drugs. Physicians assessing patients had no involvement in this. After 30 minutes patients were re-evaluated using the same scales. Scores for outcomes were averaged for each group and compared.

98 patients were enrolled with 5 exclusions (antihistamines or steroid use, or symptoms > 72 hours. The remaining 93 patients continued, 47 received diphenhydramine and 46 cimetidine.

Both groups showed significant improvement in itching and wheal intensity (p=<0.0001) and both drugs caused sedation, diphenhydramine slightly worse (p=<0.0001). There was no significant difference between groups.

Study design was sensible, using Emergency Physicians to treat a common presentation to Emergency Departments. The body of research was added to as at the time no randomised control trials existed, although case reports and open studies suggested H_2 antagonists were effective. Intra-muscular administration is not usual current practice. Outcomes were measured on an un-validated numeric scale limited by a maximum score of 3, reducing the range of scores available for continuous outcomes.

Systematic bias was avoided by all patients receiving identical assessments at identical time intervals by the same physicians. However as table 1 only compares the two groups for age, gender and previous urticaria, confounding factors such as atopy, food allergies or allergen exposure may exist. The randomisation process was simply alternation between groups, opening the possibility of selection bias as it would be easy to work out the patient's group. The randomisation and drug administration processes were separated to reduce this; however the potential for incomplete randomisation remains.

No sample size calculation is given, appearing to be a convenience sample of patients presenting in the allotted period. Therefore there is a possibility of type II error from being underpowered and 'no difference' being an erroneous conclusion. This still applies if just aiming to show equality between cimetidine and diphenhydramine.

As follow-up time was 30 minutes and the entire study took place in the Emergency Department, unsurprisingly none were lost to follow-up. This short observation time is good for assessment of rapid symptom relief, but it may have been useful to have continued the study longer to see the outcomes e.g. at 1 or 2 hours.

The Jadad score, which is a way of assessing methodological quality, for this paper is 1 out of 5.[8]

Runge *et al*

This prospective double-blind randomised study compares cimetidine, diphenhydramine, and cimetidine plus diphenhydramine for treatment of acute allergic reactions. Patients aged 18-50 years old attending two Emergency Departments in USA with acute allergic reactions (pruritis, urticaria, throat tightness or facial swelling < 12 hours) were considered. Exclusions were concurrent antihistamine or corticosteroid use, known allergy to study medications, heart disease, pregnancy or lactation, abnormal mental status, asthma or chronic obstructive pulmonary disease, patients without a telephone, use of experimental drugs within one month, patients with respiratory distress (air hunger, dyspnoea, tachypnoea, bronchospasm) or unstable vital signs (systolic blood pressure <100mmHg or pulse > 120bpm. Main outcomes were relief of pruritis and urticaria.

Participants were randomised into three groups - 50mg diphenhydramine plus placebo (DPN group), 300mg cimetidine plus placebo (CTD group) or 50mg diphenhydramine plus 300mg cimetidine (DPN + CTD group). Placebo was normal saline. Treatments were prepared, randomised and blinded by the hospital pharmacy. Administration was intra-venous.

Initial assessments on degree of urticaria, pharyngeal tissue swelling and facial swelling were completed prior to treatment by study physicians using a 110mm visual-analogue scale. Patients assessed their pruritis, throat tightness and facial swelling using identical scales.

Symptoms were deemed clinically significant if scoring more than 30mm, with insignificant symptoms excluded.

Assessment was repeated at thirty minutes. Relief of symptoms was defined as improvement of 25mm on the scale. If symptoms had improved, observation continued for 30 minutes prior to discharge. If not relieved they were discontinued from the study and treated at the physician's discretion, breaking blinding if clinically required. Successfully discharged patients were given oral preparations of study medications to be taken at 6, 12, 18 and 24 hours, with telephone follow up the next day. This follow-up data is not included in analysis.

Thirty-nine individuals were enrolled in the study. Clinically significant symptoms were pruritis (35), urticaria (33), throat tightness (10), subjective facial swelling (14), pharyngeal oedema (2) and objective facial swelling (5). Only pruritis and urticaria had sufficient numbers to be used for analysis. Thirty patients had both urticaria and pruritis.

DPN group contained 14 patients (pruritis 12, urticaria 5), CTD group 12 (pruritis 6, urticaria 8) and DPN + CTD group 13 (pruritis 12, urticaria 11). All patients completed the study. Clinically significant results were all 12 DPN patients experiencing significant relief of pruritis compared to 6 out of 10 CTD patient ($p=0.029$), DPN +CTD group improving $55.3+/-6.5$mm compared to DPN $30.7+/-6.1$mm for urticaria ($p=0.006$), and clinically significant urticaria relief was more in DPN + CTD group (11 out of 12) compared to DPN group (5 out of 11) ($p=0.027$). All other comparisons were statistically insignificant. Nine patients received further treatment (including diphenhydramine, prednisolone, epinephrine and ranitidine) outside of the study for various symptoms, occurring from the study period to 48 hours later. These patients were from all groups and whether blinding was broken is not specified.

These results suggest diphenhydramine is better than cimetidine for relief of pruritis with no advantage to combination treatment, and combination is better than diphenhydramine for urticaria relief.

This comparison of H_1 blocker against H_2 blocker and combination H_1 plus H_2 blockers is original, plus a broader scope of looking at other manifestations of acute allergic reaction. Recruitment in the Emergency Department with clear inclusion and exclusion criteria is sensible. Intra-venous drug administration is more in line with usual practice. A visual-analogue scale is appropriate for this symptom assessment and has been validated for other continuous outcomes, e.g. pain.

Patient demographics within each group are not specified making it hard to comment on effectiveness of randomisation. Symptom severity is listed for each group, showing significantly less urticaria in DPN group. Extra treatments being given risks performance bias. Two patients, one each from DPN and CTD groups, received extra diphenhydramine and prednisolone. The prednisolone is unlikely to have affected results due to time until therapeutic action, but the diphenhydramine effectively changed one patient from CTD group to DPH + CTD group. Regarding other major forms of bias there was no difference in methods of outcome assessments and no patients were lost to follow-up.

The randomisation method is not clearly described except being done by the pharmacy along with the treatment blinding. Assessments were adequately blinded as physicians were unaware of treatment groups, however accuracy could be improved if each patient was assessed by two examiners.

No sample size calculation was done. Some outcomes showed significant differences between groups, but others no difference, raising the issue of type II error. This paper again uses a 30 minute study period, but goes further than *Moscati et al* by attempting telephone follow up at 24 hours and recording extra treatments required, however this data was not used in the main analysis. No patients were lost to follow up unsurprisingly given the short nature of the study.

The Jadad score for this paper is 3 out of 5.

Lin *et al*

This prospective randomised double-blind placebo-controlled trial tests the hypothesis that combined H_1 and H_2 blockers for treatment of acute allergic syndromes will improve outcomes compared to H_1 blockade alone.

Patients aged over 18 years presenting to an American Emergency Department with acute allergic symptoms (urticaria, angioedema, unexplained stridor, pruritic rash after ingestion of food or drugs, present for <12 hours) were considered. The only exclusion criterion was pregnancy. The sample size of 100 was arbitrary.

Recruited patients were randomised to the active treatment (50mg diphenhydramine plus 50mg ranitidine) or control treatment groups (50mg diphenhydramine plus normal saline). Treatments were administered intravenously in equal volumes. Randomisation was by sealing treatment designations into locked away opaque envelopes, matched on opening with a random number assignment list. Staff who drew up treatments into identical unlabelled syringes were otherwise uninvolved with the patient.

Primary outcomes were resolution of urticaria, angioedema and erythema at 2 hours post-treatment. Extent of urticaria and erythema and presence of angioedema, wheeze, stridor and abdominal symptoms were recorded at baseline, 1 hour and 2 hours. Heart rate, blood pressure and respiratory rate were observed.

Of the 100 patients recruited, 1 was mistakenly recruited twice and 8 withdrew before any medication was given. 9 patients were treated and subsequently found to have had symptoms of longer than 12 hours. These were included on an intention to treat basis, and the patient who was recruited twice only had their first study included, leaving a total of 91 patients, 48 in experimental and 43 in control groups, with no significant differences in baseline characteristics (age, gender, ethnicity, duration of symptoms, history of allergy, eczema or asthma, NSAID use and additional symptoms).

Main results for primary outcomes were 91.7% resolution in urticaria at 2 hours in the experimental group compared to 73.8% in the control group (p=0.02) and reduction in urticaria area(p=0.02). There was no significant difference in resolution of angioedema. In patients with both angioedema and urticaria, 70.5% of the experimental group resolved compared to 46.5% (p=0.02).

This suggests combination treatment for urticaria with or without angioedema will improve symptoms over treatment with H_1 blockers alone.

This original study added to the research body as its central hypothesis had not been previously proved. It is more substantial in numbers and follow-up length compared to *Runge et al*, the only other paper looking at combinations H_1 and H_2 antagonists.

It's relevant as patients were studied in 'real life' circumstances within the Emergency Department. Study design was sensible, using the current standard treatment of H_1 blockers as the control. The intervention description was sufficient to allow reproduction.

Attempts to avoid systematic bias were good, with a detailed table showing no significant difference in group demographics. Confounding variables such as previous allergy, atopy and NSAID use were considered. The same physicians were involved for the study duration, and each patient had the same physician assessing them.

Blinding was good with drugs drawn up identically by staff otherwise uninvolved in the study so patient and physician were unaware of group allocation. Of course there is always the risk of accidental communication or observation of this process.

There was no sample size calculation as they state they had no previous studies to base their effect estimate on. This could cause a type II error of no significant difference being found for the less common outcomes such as angioedema. It was also a convenience sample dependent on the study physicians being present. However they found no predominance of particular shifts in recruitment.

Follow-up of 2 hours was adequate for management of urticaria in the Emergency Department and fits well with current practices and targets for duration of patient treatment. A longer follow-up would be preferable for more serious outcomes like anaphylaxis. Follow-up was short, within the patients' time in the hospital so none were lost to follow-up.

The Jadad score for this paper is 5 out of 5.

Watson *et al*

This randomised prospective double-blind controlled trial compares famotidine to diphenhydramine for treatment of acute urticaria. Primary outcomes were urticaria intensity and surface area, pruritis and sedation.

Patients were recruited if aged 18-55 years and presented with urticaria <72 hours to a large teaching hospital Emergency Department in California. Exclusions were allergies to study drugs, pregnancy or lactation, bronchospasm or pharyngeal oedema, unstable vital signs (systolic blood pressure <100mmHg , heart rate >120 bpm), angioedema or unable to consent.

Emergency Department physician estimated body surface area of urticaria using the 'Rule of Nines' as used for assessing burns. Wheal intensity was rated on an unnumbered visual-analogue scale ranging from 'no urticaria visible' to 'erythematous, oedematous, confluent'. Participants rated degree of pruritis and drowsiness on similar scales.

Treatments were famotidine 20mg or diphenhydramine 50mg intra-muscularly, prepared in blinded vials by the study pharmacist. Physicians re-assessed using the same scales at 30 minutes.

25 individuals were recruited, 15 received famotidine and 10 diphenhydramine. None were lost to follow-up. Both medications significantly reduced pruritis, famotidine by 36mm on the 100mm visual-analogue scale ($p < 0.0001$) and diphenhydramine by 54mm ($p < 0.0001$) with no significant difference between the groups ($0.05 < p < 0.1$). Both medications reduced intensity of urticaria significantly by 34mm ($p < 0.001$ for famotidine and $p < 0.01$ for diphenhydramine) but no significant difference between groups. For body surface area, famotidine had a significant

decrease of 20% (p<0.01) and diphenhydramine a non-significant decrease of 8% (0.05<p<0.1) but no significant difference between groups (p>0.1). There was no significant difference in sedation.

This study comes ten years after *Moscati et al* and utilises a very similar study protocol. As the earlier study failed to show a significant difference between H_1 and H_2 antagonists for treatment of acute urticaria, potentially due to being underpowered, this was an opportunity to improve. However this study is smaller with the same follow-up period, looking at whether famotidine is equally comparable to cimetidine vs diphenhydramine.

Study design is simple and easy to run in an Emergency Department; however the intra-muscular route for administration is not widely used. Outcome measures are useful, and a visual analogue scale is commonly used for symptomatic relief. It is not mentioned whether this scale was validated.

The groups show no significant difference for age, gender and symptom severity. Atopy and allergic history are not considered and could be confounding. The allocation process is not clearly described but doesn't seem to have caused systematic differences between groups. All patients received the same care and assessments from the same physicians, minimising performance bias. No patients were lost to follow-up or withdrew, and there was no difference in the outcome assessments, eliminating other potential bias sources. Blinding was good with drugs drawn into identical vials by the study pharmacist.

The main problem with this study is the sample size. In two years at a large teaching hospital only 25 patients were recruited compared to *Moscati et al* who with similar inclusion and

exclusion criteria managed nearly four times as many in a few months. A small sample in a study

showing no significant difference between the two groups could cause type II error.

A 30 minute follow up is similar to previous studies and is useful for rapid symptom relief

assessment, but it would be interesting to know if this was maintained.

The Jadad score for this paper is 4 out of 5.

Summary of Evidence

Table 4 below summarises the principle findings of these papers. All the studies are limited

by small sample sizes and potentially being underpowered, many of the results showing no

significant difference. For H_2 antagonist monotherapy, none of the studies showed a significant

improvement over H_1 antagonists except for cimetidine being less sedating than

diphenhydramine. The evidence for combination therapy is better; both papers (*Lin* and *Runge*)

showed statistically significant improvement in urticaria. *Lin et al* also showed improvement in

those patients with angioedema and urticaria, although no difference in patients with only

angioedema (but very small numbers).

In summary there is evidence that combination H_1 and H_2 antagonists will give a better

outcome in treatment of urticaria than H_1 antagonists alone. There is no evidence for the use of H_2

antagonists in other presentations of acute allergic reactions.

Personal Work

The studies looking at this topic are small so I decided to see if anything significant could be

gained by pooling the data using meta-analysis. The quality of evidence is low to moderate as

assessed using the GRADE Profiling system (table 3) however I felt there was value in this work to

see if the conclusions of the papers could be strengthened by combining them.

Table 3 *Summary of Findings*

H2 Blocker compared to H1 Blocker for Acute allergic reaction

Patient or population: Patients with acute allergic reactions
Settings: Emergency Department
Intervention: H2 Blocker
Comparison: H1 Blocker

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	H1 Blocker	**H2 Blocker**				
Change in Urticaria Intensity Visual Scale. Scale from: 0 to 100. Follow-up: 30 minutes	The mean change in urticaria intensity in the control groups was **-31 percent**[1]	The mean Change in Urticaria Intensity in the intervention groups was **0.18 standard deviations lower** (0.52 lower to 0.15 higher)		139 (3 studies)	⊕⊕⊖⊖ **low**[2,3]	
Change in Urticaria Area Body area chart. Scale from: 0 to 100. Follow-up: 30 minutes	The mean change in urticaria area in the control groups was **-8 percentage body area**[4]	The mean Change in Urticaria Area in the intervention groups was **0.59 standard deviations lower** (1.41 to 0.23 higher)		25 (1 study)	⊕⊕⊕⊖ **moderate**[2,3]	
Change in Pruritis intensity Visual analogue or numerical scale. Scale from: 0 to 110. Follow-up: mean 30 minutes	The mean change in pruritis intensity in the control groups was **59 percent**[4]	The mean Change in Pruritis intensity in the intervention groups was **0.59 standard deviations higher** (0.24 to 0.94 higher)		140 (3 studies)	⊕⊕⊖⊖ **low**[2,3]	
Sedation Numeric Scale and Visual Analogue Scale Follow-up: mean 30 minutes	The mean sedation in the control groups was **10 percent increase in sedation**[4]	The mean Sedation in the intervention groups was **0.91 standard deviations lower** (1.3 to 0.53 lower)		118 (2 studies)	⊕⊕⊖⊖ **low**[3,5]	

[1] Mean percentage improvement in urticaria intensity for control (H1 blocker) group extrapolated from the 3 studies
[2] Most evidence from studies assessed at low or unclear risk of bias however use of unvalidated clinical outcome measures and poor descriptions of randomisation processes are limitations likely to lower confidence in results. Downgrade 1 level for this.
[3] Total sample size less than 400.
[4] Percentage improvement in control group estimated from studies included
[5] Randomisation done by alternating patients in Moscati paper

Combination H1 and H2 Blockers compared to for Acute Allergic Reactions

Patient or population: Patients with acute allergic reactions
Settings: Emergency Department
Intervention: Combination H1 and H2 Blockers
Comparison:

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk **Combination H1 and H2 Blockers**				
Relief of Urticaria Clinical Improvement Follow-up: 30-60 minutes	**Low risk population[1]**		OR 0.15 (0.05 to 0.44)	76 (2 studies)	⊕⊕⊕⊖ **moderate[2]**	
	540 per 1000	**150 per 1000** (55 to 341)				
	High risk population[1]					
	790 per 1000	**361 per 1000** (158 to 623)				
Absence of Angioedema at 120 minutes Clinical findings Follow-up: mean 120 minutes	**519 per 1000**	**500 per 1000** (245 to 755)	OR 0.9286 (0.3011 to 2.8636)	49 (1 study)	⊕⊕⊕⊖ **moderate[2]**	

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High and low risks from events in control goups in 2 studies included i.e. presence of urticaria after control treatment
[2] Sample size less than 300

Figures 1 and 2 show the data analysis for outcomes studied in more than one paper. This is divided into two sections, firstly for comparison of H_1 and H_2 antagonists (*Moscati et al, Runge et al, Watson et al),* and secondly, for comparison of combination H_1 and H_2 antagonists versus H_1 antagonists (*Lin et al*, *Runge et al).* There were three groups in *Runge et al* so data was taken from the appropriate group for the comparison being made. The figures at 1 hour were used from *Lin et al* as they were closest to the 30 minute time period used in *Runge et al.*
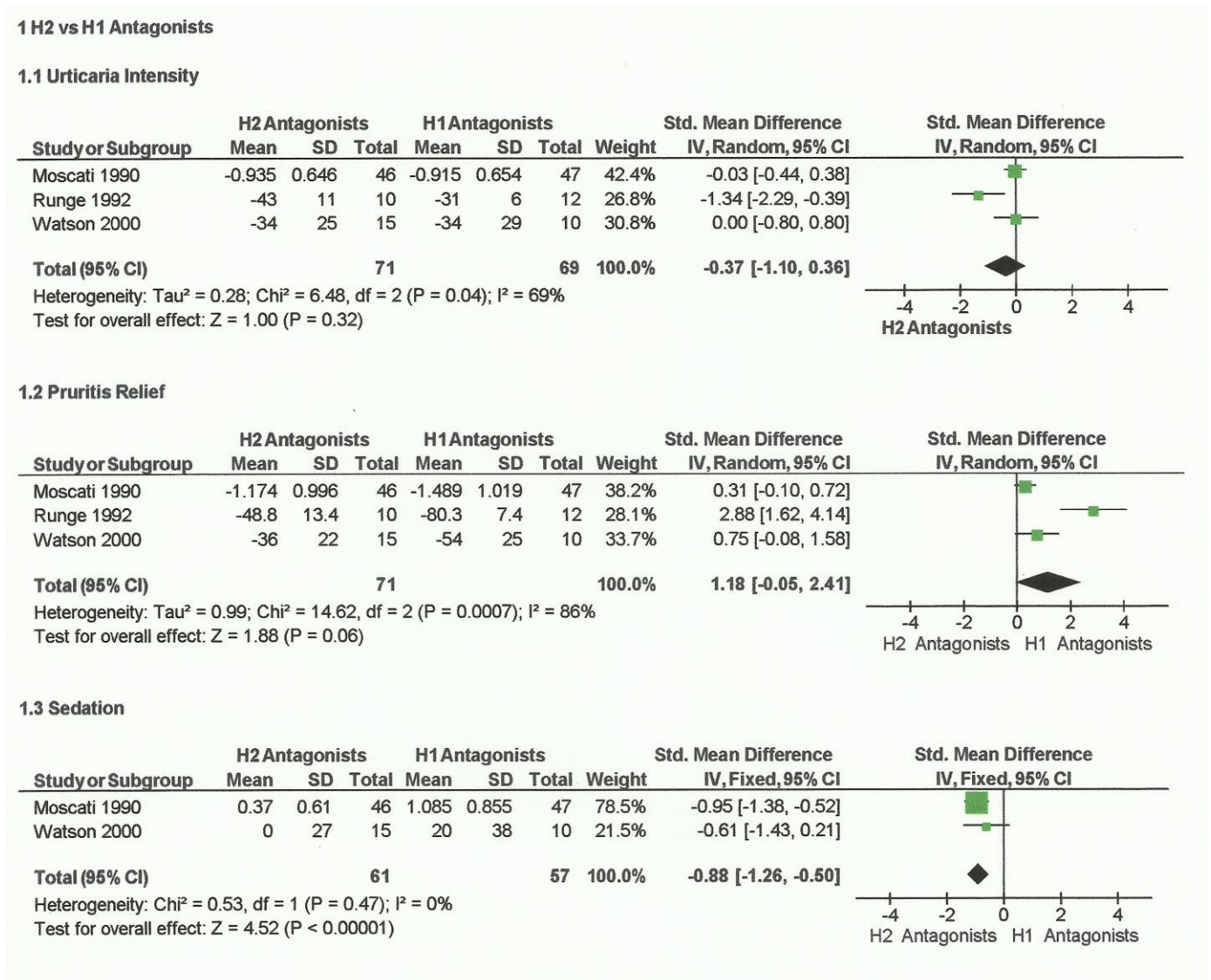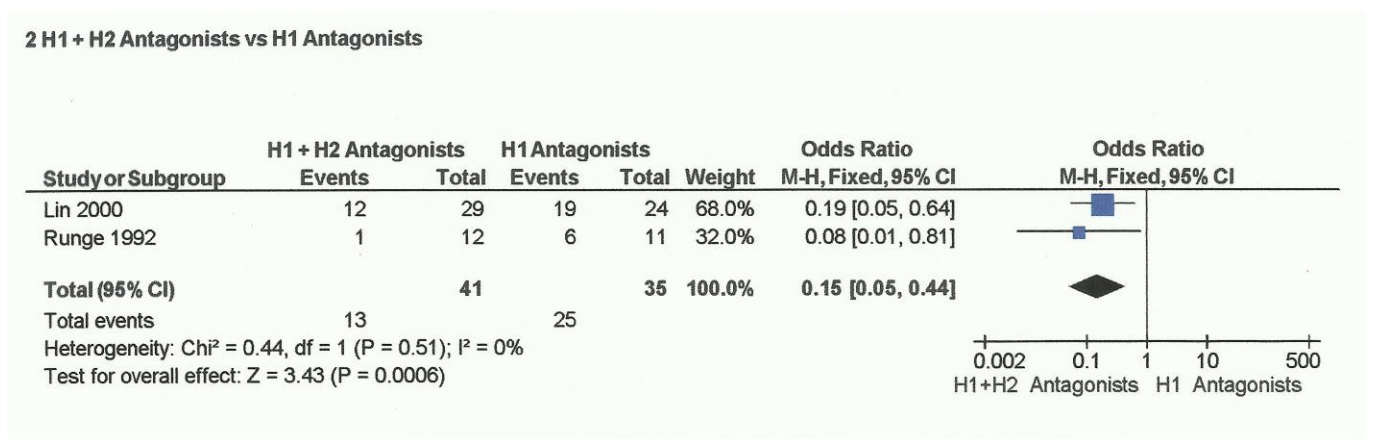
Figure 1 *Data analysis of H₁ vs. H₂ Antagonists*

1 H2 vs H1 Antagonists

1.1 Urticaria Intensity

Study or Subgroup	H2 Antagonists Mean	SD	Total	H1 Antagonists Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Moscati 1990	-0.935	0.646	46	-0.915	0.654	47	42.4%	-0.03 [-0.44, 0.38]
Runge 1992	-43	11	10	-31	6	12	26.8%	-1.34 [-2.29, -0.39]
Watson 2000	-34	25	15	-34	29	10	30.8%	0.00 [-0.80, 0.80]
Total (95% CI)			**71**			**69**	**100.0%**	**-0.37 [-1.10, 0.36]**

Heterogeneity: Tau² = 0.28; Chi² = 6.48, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 1.00 (P = 0.32)

1.2 Pruritis Relief

Study or Subgroup	H2 Antagonists Mean	SD	Total	H1 Antagonists Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Moscati 1990	-1.174	0.996	46	-1.489	1.019	47	38.2%	0.31 [-0.10, 0.72]
Runge 1992	-48.8	13.4	10	-80.3	7.4	12	28.1%	2.88 [1.62, 4.14]
Watson 2000	-36	22	15	-54	25	10	33.7%	0.75 [-0.08, 1.58]
Total (95% CI)			**71**				**100.0%**	**1.18 [-0.05, 2.41]**

Heterogeneity: Tau² = 0.99; Chi² = 14.62, df = 2 (P = 0.0007); I² = 86%
Test for overall effect: Z = 1.88 (P = 0.06)

1.3 Sedation

Study or Subgroup	H2 Antagonists Mean	SD	Total	H1 Antagonists Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Moscati 1990	0.37	0.61	46	1.085	0.855	47	78.5%	-0.95 [-1.38, -0.52]
Watson 2000	0	27	15	20	38	10	21.5%	-0.61 [-1.43, 0.21]
Total (95% CI)			**61**			**57**	**100.0%**	**-0.88 [-1.26, -0.50]**

Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 4.52 (P < 0.00001)

Figure 2 *Data analysis of combination H₁ and H₂ Antagonists vs. H₁ Antagonists*

2 H1 + H2 Antagonists vs H1 Antagonists

Study or Subgroup	H1 + H2 Antagonists Events	Total	H1 Antagonists Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lin 2000	12	29	19	24	68.0%	0.19 [0.05, 0.64]
Runge 1992	1	12	6	11	32.0%	0.08 [0.01, 0.81]
Total (95% CI)		**41**		**35**	**100.0%**	**0.15 [0.05, 0.44]**
Total events	13		25			

Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 3.43 (P = 0.0006)

When comparing H_1 and H_2 antagonists a trend is sown towards better outcomes with H_2 antagonists for urticarial intensity and degree of sedation; and for H_1 antagonists in relief of pruritis. These results are not, however, statistically significant.

For combination treatment vs H_1 antagonists in urticaria a significant improvement in outcome is shown (OR 0.15 CI 0.05-0.44). This gives an estimated range for the NNT (number needed to treat) between 2 and 6.

Difficulties were encountered due to the small number of papers and the use of different outcome measures. This was especially problematic with the *Moscati* paper as a score out of 3 was used rather than a visual analogue scale. Steps were taken to allow for the use of different outcome measures by using standard mean difference however there is a significant difference between a scale of 0-3 and 0-110. Also there is a high degree of heterogeneity between the studies and for some comparisons the confidence intervals do not overlap. Random effects analysis was used because of this but it does mean that these results are not robust. Details of the software and calculations used are in Appendix A.

Conclusion and Recommendations

The significant results of the studies and the personal work from this CTR are summarised in table 4. Although this further analysis of the available data does not support the use of H_2 antagonists alone in acute allergic reactions, it does show evidence for the use of combination treatment in urticaria. For other presentations such as angioedema, the evidence is not strong enough. It would have been interesting to look into the effects on other allergic presentations especially anaphylaxis but there is no study that looks at this clinical situation.

Table 4 *Summary of Results*

Outcome	Moscati	Runge	Lin	Watson	My Meta-analysis
H$_1$ vs H$_2$ Antagonists					
Urticaria	No significant difference	No significant difference		No significant difference	No significant difference
Pruritis	No significant difference	Significant relief with **Diphenhydramine**		No significant difference	No significant difference
Degree of sedation	Less sedation with **Cimetidine**			No significant difference	H$_2$ less sedating
H$_1$ vs H$_1$ + H$_2$ Antagonists					
Urticaria		Significant relief with **combination treatment**	Significant relief with **combination treatment**		Significant relief with **combination treatment**
Pruritis		No significant difference			
Angioedema + urticaria			Significant relief with **combination treatment**		

To obtain a significant result further study is required correctly powered and with a larger sample size encompassing a broader sample of allergic reaction patients. In the meantime I would recommend that H$_2$ antagonists be considered for treatment of urticaria in combination with H$_1$ antagonists.

Appendix A - Details of calculations and software used for personal work.

'Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011' and 'GRADEpro. [Computer program]. Version 3.2 for Windows. Jan Brozek, Andrew Oxman, Holger Schünemann, 2008' for the analysis.

Advice on the statistical models to use was gratefully received from Richard Parker at the Centre for Applied Medical Statistics at the University of Cambridge. Any mistakes are my own.

The NNT (numbers needed to treat) calculated from my meta-analysis were calculated using the following formula from the Cochrane Handbook. Firstly the assumed control group risk was calculated from the diphenhydramine groups with urticaria in the 2 papers used, as the risk of the patient still having urticaria after treatment. In *Runge,* 5 out of 11 or 54% of patients still had urticaria after treatment, in *Lin* it was 19 out of 24 or 79%. These were used as the low and high assumed control risks in the summary of findings tables and to calculate the NNT using the formula from the Cochrane Handbook.[9]

NNT = 1/(ACR-(ORxACR/1-ACR + (ORxACR)))

NNT = Number Needed to Treat
OR = Odds Ratio
ACR = Assumed Control Risk

The calculation was done using both the higher and lower ACR and the upper and lower confidence interval limits for the OR to give a range for the NNT rounded to whole numbers.

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