Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects

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Authors' objectives
The primary aim was to identify the test which are most sensitive to the effects of antihistamines, to identify a test-battery which can be used when assessing the sedative profile of antihistamines. The secondary aim was to assess the sedative potential of second generation of antihistamines using a battery of cognitive and psychomotor tests. The methods and results relating to this aim are presented below.

Searching
MEDLINE was searched from 1965 to 1997. Search terms included 'histamine H1 antagonists', 'antihistatmines', 'psychomotor performance', 'cognitive function', 'astemizole', 'loratadine', 'cetrizine', 'fexofenadine', 'mizolastine' and 'ebastine'. Only published studies and abstracts were included.

Study selection
Study designs of evaluations included in the review
Controlled studies, all studies reported in the review used a double-blind cross-over design. Single-blind cross-overs and/or parallel group comparison methods were excluded.

Specific interventions included in the review
Second line anti-histamines: Acrivastine (4-24mg), Astemizole (10-40mg), azatadine (4-8mg), cetirizine (2.5-20mg), clemastine (1-4mg), ebastine (10-30mg), fexofenadine (80-240mg), ketotifen (1-2mg), levocaastine (0.5-2mg), mequitazine (5-10mg), loratadine (10-40mg), mizolastine (5-45mg), oxatomide (30mg), tazyfylline (5-15mg), temelastine (200mg), tergenadine (20-240mg).

Intervention treatment were compared to either placebo or verum therapy. Acute and repeated dosage regimes were included. Verums (positive controls): chlorpheniramine (4-16mg), diphenhydramine (25-150mg), hydroxyzine (25-50mg), promethazine (10-30mg), tripolidine (2.5-15mg) these were exclusively used as verums. Clemastine and ketotifen were used as both comparators and positive controls. Seven traditional antihistamines () were included as these were used as positive controls.

Participants included in the review
Healthy volunteers.

Outcomes assessed in the review
Sedation (categorised as psychomotor performance, sensorimotor co-ordination speed, CNS arousal, information processing, memory, sensory skills, motor ability, physiological) as measured by both objective and subjective assessment. Of particular interest were studies using standardised, quantitative methods of defining both objective and subjective drug-induced effects on sedation, psychomotor performance and cognition.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or exactly what data were extracted from the studies.

For each drug and test dose, results listed as ‘impairment’, or ‘no impairment’ for each test. If a statistically significant difference (p<0.05) was found between the test drug and placebo on a specific test indicating disturbed CNS activity then the results were listed as impairment. For each drug the number of discrete tests in which significant impairment was reported were totalled.

**Methods of synthesis**

**How were the studies combined?**

The risk: benefit ratio for each antihistamine was calculated according to the formula I/NI, where I= number of tests where significant impairment of performance was found and NI = number of tests where no impairment was detected. This ratio represented the likelihood that a given antihistamine will cause sedative effects.

**How were differences between studies investigated?**

The authors do not state how differences between the studies were investigated.

**Results of the review**

There were 55 placebo and verum (positive control) controlled studies, using a randomised, double-blind cross-over design (number of participants not stated).

Results were only provided for selected antihistamines (authors do not state what criteria were used in the selection process):

Risk benefit ratio for all tests combined (number of tests showing no impairment, no of tests showing impairment):

Fexofenadine: 0.00 (31, 0).
Ebastine: 0.00 (14, 0).
Cetirizine: 0.21 (70, 15).
Loratadine: 0.29 (38, 11).
Mizolastine: 0.50 (34, 25).
Chlorpheniramine: 7.67 (3, 23).
Diphenhydramine: 27.50 (2, 55).
Triprolidine: 60.00 (1, 60).

Risk benefit ratio for subjective tests:

Fexofenadine: 0.00 (6, 0).
Ebastine: 0.00 (5, 0).
Cetirizine: 0.32 (22, 7).
Loratadine: 0.07 (12, 1).
Mizolastine: 0.40 (5, 2).
Chlorpheniramine: Not done (0, 9).
Diphenhydramine: Not done (2, 19).

Triprolidine: 14.0 (1, 14).

Risk benefit ratio objective tests:

Fexofenadine: 0.00 (25, 0).

Ebastine: 0.00 (9, 0).

Cetirizine: 0.17 (48, 8).

Loratadine: 0.38 (26, 10).

Mizolastine: 0.52 (29, 15).

Chlorpheniramine: 4.67 (3, 14).

Diphenhydramine: 18.0 (0, 36).

Triprolidine: Not done (0, 46).

**Authors' conclusions**

Using this battery of cognitive and psychomotor tests, it is evident that only a very limited number of antihistamines can claim to be virtually free of both objective and subjective sedative effects, although the second generation of antihistamines are generally less impairing than the original ones when prescribed at their recommended doses.

**CRD commentary**

A poor review of the area. A literature search was conducted, however, important studies could have been missed as only one database was searched and only published studies and abstracts were included, thus the results may be subject to publication bias. The authors do not state whether there were restrictions on language of publication. Inclusion criteria were clearly stated but individual study details were not provided. The authors do not conduct any form of validity assessment, and they do not state how and what data was extracted from the primary studies, there are no individual study details provided or information on the number of participants included in the studies. The analysis used was not a standard method, however, it does appear to be an appropriate method of combining the data, although heterogeneity was not investigated or discussed. Because of the lack of details about studies and the lack of assessment of heterogeneity it is not clear if it was appropriate to combine the studies. The authors conclusions appear to be supported by the data presented, although these results should be interpreted with caution because of the limitations discussed above.

**Implications of the review for practice and research**

The authors did not state any implications for practice or further research.

**Bibliographic details**

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