

Psychometric aspects of antihistamines

Hindmarch I. Psychometric aspects of antihistamines.
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Sedation is common with the so-called “classical” antihistamines, but the newer compounds are said to be free of central nervous system (CNS) side-effects (1). The literature was extensively reviewed in order to identify those psychometric variables and conditions which have proved to be sensitive to the CNS effects of antihistamines. It is hoped that this review will allow the formulation of a series of guidelines for both researchers deciding on the methodology of future trials, and readers assessing the validity of a particular volunteer study with antihistamine(s).

The data used for this current presentation have been published, in full, elsewhere (2); what follows is an extension of the previous analysis to find a straightforward method of determining the relative sedative potential of different antihistamines.

Studies have been performed on the pharmacodynamics of some 37 different antihistamines (Table 1) over a wide range of dose regimens.

The psychometrics used are also varied and cover both objective aspects of performance (CNS function, and general psychological abilities), as

well as subjective assessment of sedation, sleep, etc. (Table 2).

For the sake of completeness and for those who seek original references for the data used in this paper, the bibliographic sources are given below in Table 3.

The psychometric methods used to determine adverse effects have been identified as either “objective” or “subjective”. Objective tests require psychomotor performance of some sort by the subject. The performance measure is a physical one: time, number, frequency, etc. Subjective tests require a subject to indicate an impression, feeling, or opinion, usually on a pencil-and-paper questionnaire or visual analogue rating scale.

For both objective and subjective assessments, the number of discrete tests in which significant

Table 1. Antihistamine drugs studied for psychometric effects

Placebo/verum-controlled	Placebo-controlled
Acrivastine (4–16 mg)	Dimethindene (2.5 mg)
Astemizole (10–40 mg)	Diphenhydramine (25–75 mg)
Azatadine (4–8 mg)	Diphenylpyraline (2 mg)
Brompheniramine (4–12 mg)	Hydroxyzine (20 mg)
Cetirizine (5–20 mg)	Ketotifen (1 mg)
Chlorpheniramine (4–16 mg)	Levocabastine (0.5 mg/ml)
Clemastine (1–2 mg)	Loratadine (10–40 mg)
Dimethindene (50–100 mg)	Mebhydrolin (50 mg)
Diphenhydramine (50–100 mg)	Meclastine (1–3 mg)
Hydroxyzine (25 mg)	Mequitazine (5 mg)
Ketotifen (1 mg)	Phenindamine (25 mg)
Levocabastine (0.5–2 mg/ml)	Pheniramine (50 mg)
Loratadine (10–40 mg)	Promethazine (50 mg)
Mequitazine (5–10 mg)	SCH 12169 (2 mg)
Oxatomide (30 mg)	Terfenadine (20–240 mg)
Tazifylline (5–15 mg)	Trimeprazine (10–20 mg)
Temelastine (100 mg)	Tripelennamine (25–50 mg)
Terfenadine (60–240 mg)	Triprolidine (5 mg)
Triprolidine (1.25–10 mg)	

Table 2. Tests used for assessing effects of antihistamines on performance (examples)

Psychomotor performance (actual car driving/steering)
Sensorimotor coordination (adaptive tracking/pursuit)
Reaction time (choice/simple reaction time)
CNS arousal (critical flicker fusion)
Information processing (mental arithmetic/verbal fluency)
Memory (short-term/visual memory)
Sensory skills (spatial perception)
Motor ability (pegboard)
Physiological (continuous-EEG/multiple sleep latency)
Subjective (visual analogue and rating scales)

Table 3. References for original data sources

Astemizole	3–13
Azatadine	14–17
Cetirizine	1, 18–30
Chlorpheniramine	1, 6, 7, 14, 15, 31–34
Clemastine	9, 12, 14, 17, 34–39
Diphenhydramine	5, 15, 18, 40–49
Loratadine	24, 28, 29, 48, 50–51
Terfenadine	1, 3, 4, 22, 25, 27, 30, 32, 34, 45, 46, 49, 52–54
Triprolidine	1, 3, 4, 22, 31, 33, 35, 50, 51, 53–59

Table 4. Rank sedative effects of selected antihistamines (I/Ni ratio) (verum control and placebo and placebo alone)

Table 4A: I/Ni < 0.1

	Dose (mg)	No. of tests showing no impairment (NI)		No. of tests showing significant impairment (I)	
		Obj.	Sub.	Obj.	Sub.
Astermizole	10	27	9		
	20	3	1		
	30	28	8	1	
	40	1	1		
Ratio I/Ni: Total=0.01. Subjective=0.00. Objective=0.02.					
Azatadine	1	5	1		
	2	11	3		
	3	6	1		
	4	6	2		
	8	6	2	1	
Ratio I/Ni: Total=0.02. Subjective=0.00. Objective=0.03.					
Terfenadine	20	2	1		
	60	53	15	3	
	120	28	4		
	180		1		
	240	8	2	1	
Ratio I/Ni: Total=0.04. Subjective=0.00. Objective=0.04.					
Cetirizine	2.5		1		
	5	5	4		
	10	29	17	4	
	20	10	8	3	
Ratio I/Ni: Total=0.09. Subjective=0.00. Objective=0.16.					

Table 4B: I/Ni > 0.1

Loratadine	10	23	5		
	20	10	2		1
	40	8	3	4	1
Ratio I/Ni: Total=0.12. Subjective=0.20. Objective=0.10.					
Clemastine	1	30	12	5	1
	2	7	1	3	1
	3	7	1		
Ratio I/Ni: Total=0.17. Subjective=0.14. Objective=0.18.					
Diphenhydramine	25	3	1		
	50	30	2	13	9
	75	3			
	100	6			1
Ratio I/Ni: Total=0.51. Subjective=3.33. Objective=0.31.					
Chlorpheniramine	2			1	
	4	11	4	4	2
	10	1		1	1
	16			1	1
Ratio I/Ni: Total=0.59. Subjective=1.00. Objective=0.58.					
Triprolidine	1.25	2	1	2	
	2.5	2	2	6	1
	5	7	1	18	4
	7.5	3		2	1
	10	9	3	22	6
Ratio I/Ni: Total=2.07. Subjective=1.71. Objective=2.17.					

impairment was reported was counted. The risk/benefit ratio for each H₁-antagonist was then calculated according to the following formula:

$$\frac{I}{NI}$$

where I=the number of tests where significant impairment of performance was found, and NI=the number of tests where no impairment was detected. This calculation gives an impairment/non-impairment ratio which represents the likelihood that a given H₁-antagonist will cause adverse (sedative) effects. The more impairment observed with a given drug, the greater is the value of the ratio. Conversely, an H₁-antagonist with a good benefit/risk ratio has a value close to zero.

Using data from both verum (i.e., positive internal control) and placebo, and placebo-alone studies, we found that antihistamines differ in the extent to which they produce sedation (Table 4A and 4B).

Using the above formula to calculate the risk/benefit ratio for a selection of antihistamines, it is possible to rank these drugs in order of increasing adverse effects. Table 4A identifies four substances, astemizole (10–40 mg), azatadine (1–8 mg), cetirizine (5–20 mg), and terfenadine (20–240 mg), as particularly free from unwanted CNS activity (i.e., with an I/Ni ratio of less than 0.1). An H₁-antagonist with an I/Ni ratio of less than 0.1 could be considered to have negligible sedative effects in terms of its effect on normal daily activity. In contrast, the older generation and other antihistamines with I/Ni ratios in excess of 0.1 (Table 4B) all show appreciable sedative effects. The most impairing has an I/Ni ratio 200 times greater than the least.

However, it could be argued that placebo controls alone are not sufficient and that the validation, by the presence of sedation produced by a verum, of pharmacodynamic studies of antihistamines is a necessary condition, especially when claims are to be made that a particular H₁-receptor blocker is without measurable CNS effect likely to interfere with the performance of everyday tasks.

Table 5 presents the I/Ni ratios derived from studies using both verum and placebo controls. These must be seen as a more sensitive measure, but there are fewer of them in the literature.

The results presented here are self-evident: psychometric tests enable the discrimination of those sedative H₁-receptor antagonists from others which have similar profiles of clinical effectiveness, but little or no effect on important aspects of performance associated with everyday activities.

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Table 5. Rank sedative effects of selected antihistamines using I/Ni ratio from studies with both verum and placebo controls

	Dose (mg)	No. of tests showing no impairment (NI)		No. of tests showing significant impairment (I)	
		Obj.	Sub.	Obj.	Sub.
Asterizole	10	10	3		
	20	3	1		
	30	1			
	40	1	1		
Ratio I/Ni: Total=0.00. Subjective=0.00. Objective=0.00					
Cetirizine	2.5				
	5	5	3		
	10	18	7		
	20	9	7	1	
Ratio I/Ni: Total=0.02. Subjective=0.00. Objective=0.03.					
Terfenadine	20				
	60	44	10	2	
	120	22	2		
	180				
	240	6	1		
Ratio I/Ni: Total=0.02. Subjective=0.00. Objective=0.03.					
Azatadine	1				
	2				
	3				
	4	6	2		
	8	6	2	1	
Ratio I/Ni: Total=0.06. Subjective=0.00. Objective=0.08.					
Loratadine	10	16	2		
	20	10	2		
	40	8	2	3	
Ratio I/Ni: Total=0.08. Subjective=0.00. Objective=0.09.					
Chlorphen-iramine	2				
	4	11	4	2	1
	10	1		1	1
	16			1	1
Ratio I/Ni: Total=0.44. Subjective=0.75. Objective=0.33.					
Clemastine	1	5	3	3	
	2	1		3	1
	3				
Ratio I/Ni: Total=0.78. Subjective=0.33. Objective=1.00.					
Diphen-hyramine	25				
	50	18		10	8
	75				
	100	6			1
Ratio I/Ni: Total=0.78. Subjective=nil. Objective=0.42.					
Triprolidine	1.25	2	1	2	
	2.5	2	2	6	1
	5	7	1	13	3
	7.5	3		2	1
	10	9	3	22	6
Ratio I/Ni: Total=1.87. Subjective=1.57. Objective=1.98.					

Round-table discussion

Juhlin: Increasing the dose of an antihistamine often results in a greater sedative effect. Were your ranking figures based on the regular dose or on increased doses?

Hindmarch: It is difficult to find a dose of an antihistamine that is comparable across the board. The argument is a simple one; if it is a nonsedating antihistamine, increasing the dose should not necessarily increase sedation. However, for the purposes of this study, all doses, be they high or low, have been included.

Simons: Ideally, if we knew the equivalent dose for efficacy, it would be the best way to look at antihistamines in a ranking study. We think we know most of the doses for these medications and of course we also have those recommended by the manufacturer.

Hindmarch: If you give me those figures, i.e., the appropriate doses, we could put the adverse effects in ranking order based on comparative studies. The question of relevant dose is a problem; for example, terfenadine is recommended to be given at 60 mg, but quite often in the UK the mean dose is far in excess of that.

Simons: Officially, there are two recommended doses for terfenadine, i.e., 60 mg twice daily or terfenadine 120 mg once daily. We did look at both these doses in one study. This makes a difference in interpretation of adverse effects. Many of the single-dose studies are done at peak serum concentrations and therefore, presumably, at peak CNS concentration, i.e., 2–3 h. Your study showed no difference between 60 and 180 mg terfenadine – you didn't look at 120 mg terfenadine?

Hindmarch: No, we looked at 60, 180, and 240 mg terfenadine.

Simons: You did find adverse reactions with 240 mg terfenadine?

Hindmarch: Yes, but that study is not included here.

Simons: Because it was an alcohol interaction study?

Hindmarch: Yes, we found that when alcohol interaction is included, the design of the study changes. You are not really interested in absolute impairment, but whether coadministration makes your

performance measure worse. The problem was that we decided to put every significant result of the study into the database. This was the only way we could cope with the fact that virtually every study in the literature is unique. For example, I don't think we came across two studies that used the same test times. This illustrates the difficulty, and in no way am I trying to give these results pseudo-statistical validity. It does mean that if you apply the same criteria to each substance you do come up with a ranking order that does fit with the general experience of these compounds.

Simons: I'm fascinated by your approach to this problem because in 1992 we were asked to do an overview of adverse effects of H₁-antagonists which included cardiac as well as CNS effects. I chose only to look at the more recent studies, but you have gone much further back in the literature. Despite this, it is interesting to note that our results are comparable [Simons FER. H₁-receptor antagonists. Comparative tolerability and safety. Drug Safety 1994; 10: 350–80]. You mentioned that there were no subjective adverse effects for terfenadine. I wonder whether your review included the Alford et al. [1] study in which the EEG data were clean but some subjective effects of sedation were reported. Did you include this in your database?

Hindmarch: No, even though it was from my group. It is only published in *Medical Science Research* so it wasn't peer reviewed, although it does satisfy the other criteria such as inclusion of placebo and verum control.

Simons: It only had six subjects though.

Hindmarch: Yes, but that is acceptable for EEG, although it's too low for subjective testing.

Simons: Are somnolence and sedation the same thing since most of the literature talks about sedation? The FDA [US Food and Drug Administration] and other regulatory bodies require us to address the issue of somnolence.

Hindmarch: I know Ed Volkerts will talk on this point, but, briefly, sedation is what we measure by psychometric tests, and anything else is a word for a vague subjective impression.

Simons: Because patients use words like "I'm tired" or "I'm sleepy".

Hindmarch: This is a very important point; basically, sedation is measured by a battery of psycho-

metric tests. Any other words are used by patients to tell their doctors about their subjective experiences, words that are not used in science.

Simons: Can you explain why triprolidine, the H₁-antagonist most likely to have adverse CNS effects, is so different from acrivastine, of which there are few studies?

Hindmarch: I don't really know; it seems that triprolidine in time-capsule form loses most of its sedative effect.

Simons: Because you don't get the same peak serum levels.

Hindmarch: Certainly, the noncapsule formulation of triprolidine is, in our hands, the most sedative compound. Why it's different from acrivastine, I don't know.

Simons: Do you think it's reasonable to call acrivastine a nonsedating antihistamine on the basis of so few studies?

Hindmarch: There are only a few studies, but it does look as though that may be the case. I think acrivastine is moving toward being considered a nonsedating antihistamine.

Simons: I wonder whether you have any unpublished data on this?

Hindmarch: I've seen one study as a reviewer which supports the idea of acrivastine as a nonsedating antihistamine. I would like to see more data in this regard and also for loratadine, which is also very poorly represented in the literature.

Simons: The whole problem is that we cannot talk about adverse effects "in a vacuum". We also have to relate these to the efficacy of a drug, and in most studies this has not been done. For example, there are several studies with cetirizine in which its well-proven ability to block histamine- or antigen-induced wheal-and-flare reaction in the skin has been compared with its adverse CNS effects. Many of the studies in your database only looked at the central effect.

Hindmarch: Yes, it's clear that cetirizine is far superior in terms of its potent ability to suppress the wheal-and-flare reaction in the skin. Again, it is a matter of collating these findings with our study on adverse effects. There may be some interesting correlations.

Hindmarch

Simons: I really do think that it is the ratio or therapeutic index of antihistamines that is the main interest for us.

Broide: How accurate is 24-h EEG monitoring in detecting sedation? I wonder whether it is an accurate way of classifying sedating and nonsedating antihistamines?

Hindmarch: We think that 24-h EEG monitoring is an excellent way to determine the sedating potential of a drug. The small crossover study that we have just talked about where we only had six volunteers, which is a good number for a sleep laboratory, is a case in point. We have used this technique to look at the CNS effects of many substances, including antihistamines, and I now feel that this technique is very reliable. I think you will find that the majority of sleep laboratories in the USA are happy for their patients to go home with a 24-h EEG rather than have them spend a night in the lab. The technology is now so good that an EEG can tell you whether a person is asleep or awake. The main advantage is that you can constantly monitor your subjects over a 12-h or even 24-h period for sedation by antihistamines. Psychometric tests are only discrete measures at particular points in time. We have also used wrist actigraphs and get good results as to whether a patient is sedated or not. The ideal study would use these methodologies to look at the effect of a range of doses, but these would not be cheap or easy to perform.

Broide: They may not be cheap, but they would be the most accurate and worthwhile studies.

Hindmarch: Yes, one other problem is the variability in terms of subject response to the CNS effects of antihistamines. It is impossible to sedate some patients with even the most sedating first-generation antihistamines. It is also important to look for sedation over a 12-h period, or even better 24-h, because if a drug makes you tired by day it will disrupt your sleep at night.

Juhlin: Does the initial state of excitement of your subjects before testing influence the results? and, secondly, do you ever see other effects on your EEG as well as sedation; again, for example, excitement?

Hindmarch: We have never looked at our EEG for paradoxical excitement. The problem is that it is very difficult to get a base-line measurement of excitement; we only tend to look at somnolence.

Juhlin: I had in mind that the reaction of your subjects when they first see all your complex equipment might influence their subsequent reactions when tested.

Hindmarch: All our subjects are trained before testing so this isn't a problem.

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