

Comments on Chlorphenamine from Expert Member

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS	
<input type="checkbox"/> chlorphenamine <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Injection: 10 mg (hydrogen maleate) in 1-ml ampoule. Oral liquid: 2 mg/5 ml. Tablet: 4 mg (hydrogen maleate). <input type="checkbox"/> >1 year. <input type="checkbox"/> Review of diphenhydramine to assess comparative efficacy and safety with chlorphenamine as a possible preferable alternative.

Comment 1: Regarding the comparative efficacy and safety between chlorphenamine and diphenhydramine, if there are any, will not be sufficient for recommending a preferable choice. Safety data is likely to be a class effect with anticholinergic activities as a major factor along with somnolence effects, of which diphenhydramine seems to have a disadvantage.

Discussion:

1. Micromedex 2007 search. There was no comparison between chlorpheniramine and diphenhydramine published in the database.
2. Pubmed search. Using the term chlorpheniramine AND diphenhydramine and limited the search to clinical trials i.e. (("chlorpheniramine"[MeSH Terms] OR chlorpheniramine[Text Word]) AND ("diphenhydramine"[MeSH Terms] OR diphenhydramine[Text Word])) AND Clinical Trial[ptyp], only 12 articles were found (appendix 1) with the following retrievable relevant summaries. The only accountable difference between the two is that diphenhydramine is more sedating than chlorphenamine.

Jaffe JH, Bloor R, Crome I, Carr M, Alam F, Simmons A, Meyer RE. A postmarketing study of relative abuse liability of hypnotic sedative drugs. Addiction. 2004 Feb;99(2):165-73.

The antihistamines (**chlorpheniramine, diphenhydramine**) **had lowest abuse liability profiles**, while the antidepressants (amitriptyline, fluoxetine, trazadone) and non-benzodiazepine hypnotics (zolpidem, zopiclone) had similar profiles.

Witek TJ Jr, Canestrari DA, Miller RD, Yang JY, Riker DK. Characterization of daytime sleepiness and psychomotor performance following H1 receptor antagonists. Ann Allergy Asthma Immunol. 1995 May;74(5):419-26.

The general rank order of (soporific) effects was diphenhydramine (50 mg), followed by diphenhydramine (25 mg), followed by chlorpheniramine (4 mg). **Greater soporific effects from diphenhydramine** relative to chlorpheniramine ($P < .05$) was observed.

Note. Although not relevant to children, but it is worth mentioning, subjects that took diphenhydramine had the poorest driving performance, followed by alcohol. *Weiler JM, Bloomfield JR, Woodworth GG, et al. Effects of fexofenadine, diphenhydramine, and alcohol performance: a randomized, placebo-controlled trial in the Iowa Driving Simulator. Ann Intern Med 2000; 132(5): 354-363.*

von Maur K. Antihistamine selection in patients with allergic rhinitis. Ann Allergy. 1985 Sep;55(3): 458-62.

The antihistamine products in order of increasing frequency of significant **side effects** were: trimetoprim, **chlorpheniramine**, hydroxyzine, **diphenhydramine**, and triproleamine. The order of antihistamine **preference by the patients** was **chlorpheniramine (27%)**, **diphenhydramine (22%)**, triproleamine (20%), hydroxyzine (16%), and trimetoprim (14%).

Long WF, Taylor RJ, Wagner CJ, Leavengood DC, Nelson HS. Skin test suppression by antihistamines and the development of subsensitivity. J Allergy Clin Immunol. 1985 Jul;76(1):113-7.

The suppression of skin test reactivity by single doses of six antihistamines was measured before and after a period of daily antihistamine ingestion in 18 subjects. Single doses of hydroxyzine, 50 mg; **chlorpheniramine, 16 mg**; and promethazine, 50 mg; **induced significant suppression of skin test** reactivity at 2 hr, whereas the suppression produced by triproleamine, 100 mg; **diphenhydramine, 50 mg**; and cyproheptadine, 16 mg; **did not differ significantly from that produced by placebo.**

Note. DDD of chlorpheniramine and diphenhydramine are 12 mg. and 200 mg. respectively. For single dose test, should 4 mg of chlorpheniramine (instead of 16 mg.) be compared with 50 mg. of diphenhydramine?

Comment 2: The Subcommittee requested a review of diphenhydramine to assess the comparative efficacy and safety with chlorphenamine, as it may be applicable to a broader age range of children than chlorphenamine. After reviewing available data, it was found that the age limit of diphenhydramine injection and chlorphenamine injection was the same i.e. 1 month. Additionally, diphenhydramine liquid in an elixir form may contain as much as 14% of alcohol (PAI Pharmaceutical Associates, Inc.) and 52 elixir products (not all of them contain alcohol) are available in the US. (Micromedex 2007). In contrast, only 8 products of chlorphenamine liquid in an elixir form are available in the US, and none of them are single ingredient chlorphenamine (Micromedex 2007).

Discussion:

1. In the US, diphenhydramine injection is recommended to be used for infant age > 1 month, while oral form is used in children age > 2 years.

Pediatric Patients

Other than premature infants and neonates: 5 mg/kg/24 hr or 150 mg/m²/24 hr. Maximum daily dosage is 300 mg. Divide into four doses, administered intravenously at a rate generally not exceeding 25 mg/min, or deep intramuscularly.

Source PDR for diphenhydramine Injection USP.

2. In the UK, chlorphenamine injection is licensed for use in infant age > 1 month, while oral form is licensed for use in infant age > 1 year.

Chlorphenamine injection , SPC from the eMC

Link Pharmaceuticals Ltd

Horsham
West Sussex
RH12 1AH

Chlorphenamine injection

Age	Dose		
1 month to 1 year			0.25mg/kg
1 to 5 years	2.5mg to 5mg	OR	0.20mg/kg
6 to 12 years	5mg to 10mg	OR	0.20mg/kg
12 to 18 years	10mg to 20mg	OR	0.20mg/kg



Dosage:

Use the two-headed spoon provided.

Age	Dosage	Maximum Daily Dose
1-2 years	One small 2.5 ml spoonful twice daily	2 small 2.5 ml spoonfuls (5 ml)
2-6 years	One small 2.5 ml spoonful every 4-6 hours	6 small 2.5 ml spoonfuls (15 ml)
6-12 years	One large 5 ml spoonful every 4-6 hours	6 large 5 ml spoonfuls (30 ml)
Adults and children over 12 years	Two large 5 ml spoonfuls (10 ml) every 4-6 hours	12 large 5 ml spoonfuls (60 ml)

Children under 12 months: Not recommended.

Comment 3: Regarding the square box listing of chlorphenamine. The Subcommittee recommended that these medicines be reviewed as chlorphenamine is not registered for children under 1 year of age and may not be the best indicative drug for this class. After reviewing available data, when compared approval indications for each of the medicines in this class, chlorphenamine has the most coverage, is available in both oral and parenteral form and approved to be used in infant age 1 month for parenteral route (chlorphenamine injection – Link Pharmaceutical Ltd.). Should the square box be lifted off from chlorphenamine?

1. US FDA and UK approval indications for each of the medicines in this class are listed in the Table below. Dimetindene (R06AB03), Pheniramine (R06AB06), Dexbrompheniramine (R06AB06) and Talastine (R06AB07) are not included in the table because of poor availability, especially outside of the EU. Data scarcity is also a problem.

R06AB Substituted alkylamines	Age	AC	AR	AP	AE	DR	DS	HF	IN	UR
Brompheniramine (R06AB01) US PD	2 yr ¹	✓	✓	✓	✓					✓
Brompheniramine (R06AB01) UK				Not available						
Dexchlorpheniramine (R06AB02) US	2 yr ²	✓	✓	✓	✓					✓
Dexchlorpheniramine (R06AB02) UK				Not available						
Chlorphenamine (R06AB04) US	2 yr ³	✓	✓	✓						τ
Chlorphenamine (R06AB04) UK PD	1 mo ⁴				✓	✓	✓	✓	✓	✓

US = The United State of America, UK = The United Kingdom, PD = Parenteral Dose,

¹ For oral drops, approval age is 1 month.

² No parenteral dose is available in the US

³Oral dose. For subcutaneous route dosage is available for children age > 6 and IM or IV routes dosages are available only for adults and adolescents.

⁴For oral syrup, approval age is 1 year.

AC = Allergic Conjunctivitis, AR = Allergic Rhinitis, AP = Anaphylaxis, AE = Angioedema, DR = Desensitisation reactions, DS = Drug and Serum reactions, HF = Hay Fever, IN = Insect bites and stings, UR = Urticaria,

✓ = approved indications τ = not-FDA-approved indications Blank = not mentioned

Source: Gold Standard. Clinical Pharmacology CD-ROM. 2007 and Medicines.org.uk (eMC)

Comment 4: When comparing licensed indications between chlorphenamine and diphenhydramine, it was found that diphenhydramine had been approved with fewer indications. Availability is more limited than chlorphenamine. Combining comment 3 and comment 4, chlorphenamine should still be listed in the EML

Discussion

1. Below is the Table summarizing licensed indications for diphenhydramine in the US. (Abbreviations are the same as in the table appeared in comment 3 above.

R06AA Amino alkyl ethers	Age	AC	AR	AP	AE	DR	DS	HF	IN	UR
Diphenhydramine (R06AA02) US PD	1 mo ¹		✓	✓			✓			✓
Diphenhydramine (R06AA02) UK				Not available						

¹Diphenhydramine injection is recommended to be used for infant age > 1 month, while oral form is used in children age > 2 years.

Comment 5: The lowest dose recommended for chlorphenamine for children (1 month-2 years) in the BNF-C (2006) is 1 mg twice daily. The subcommittee endorsed the inclusion of chlorpheniramine liquid formulation in the EML. This is quite contradictory to the decision not to include ibuprofen liquid in the EML. The discussion below will show that ibuprofen suspension should be listed in the EML for children.

Discussion:

1. Chlorphenamine tablets are usually scored, while ibuprofen tablet are rarely scored. Dividing ibuprofen tablets for use in small children is not practical.



Chlorphenamine Tablets



Ibuprofen Tablets

2. Chlorphenamine is readily soluble in water, while ibuprofen does not dissolve in water at all. After dividing the tablet, preparing ibuprofen into solution is not possible, making it impractical.

3. The lowest dose recommended for chlorphenamine in children (1 month-2 years) in the BNF-C (2006) is 1 mg twice daily which is $\frac{1}{4}$ of a tablet, and this is do-able. The smallest tablet of ibuprofen listed in the EML is 200 mg. (almost always unscored, insoluble in water) and the dosage for infant is 5 mg/kg. Therefore, infants weighing less than 10 kgs should take less than 50 mg. of ibuprofen, which is smaller than $\frac{1}{4}$ of a tablet, actually for an infant who weighs 4 kgs the calculated dose is 20 mg. which is $\frac{1}{10}$ of a tablet, this is undo-able.

4. In the area where parenteral ibuprofen is not available (such as Thailand), ibuprofen suspension has been used successfully to close the PDA. This is confirmed by the work of Aly et al. who compared oral ibuprofen suspension (OIS) at 5 mg/kg and IV indomethacin and concluded that oral ibuprofen could be an easy-to-administer and efficacious alternative in the treatment of PDA.

Aly H, Lotfy W, Badrawi N, Ghawas M, Abdel-Meguid IE, Hammad TA.
Oral Ibuprofen and ductus arteriosus in premature infants: a
randomized pilot study. Am J Perinatol. 2007 May;24(5):267-70. Epub
2007 May 4.

5. My suggestion. Ibuprofen suspension should be listed in the EML for children. A warning statement about improper use of ibuprofen suspension must be in place, such as "Paracetamol is the drug of choice for fever and pain in children. For young children, if deemed necessary, ibuprofen suspension should be used cautiously, especially in the area where hemorrhagic fever is endemic. Severe bleeding may occur."

Appendix 1

Articles retrieved from Pubmed using (("chlorpheniramine"[MeSH Terms] OR chlorpheniramine[Text Word]) AND ("diphenhydramine"[MeSH Terms] OR diphenhydramine[Text Word])) AND Clinical Trial[ptyp] as the search strategy.

- 1: Jaffe JH, Bloor R, Crome I, Carr M, Alam F, Simmons A, Meyer RE.
A postmarketing study of relative abuse liability of hypnotic sedative drugs.
Addiction. 2004 Feb;99(2):165-73.
PMID: 14756709 [PubMed - indexed for MEDLINE]
- 2: Simons FE, Fraser TG, Maher J, Pillay N, Simons KJ.
Central nervous system effects of H1-receptor antagonists in the elderly.
Ann Allergy Asthma Immunol. 1999 Feb;82(2):157-60.
PMID: 10071518 [PubMed - indexed for MEDLINE]
- 3: Lang AE.
Antihistaminics in idiopathic dystonia.
Arch Neurol. 1996 May;53(5):405. No abstract available.
PMID: 8624213 [PubMed - indexed for MEDLINE]
- 4: Witek TJ Jr, Canestrari DA, Miller RD, Yang JY, Riker DK.
Characterization of daytime sleepiness and psychomotor performance following H1 receptor antagonists.
Ann Allergy Asthma Immunol. 1995 May;74(5):419-26.
PMID: 7749974 [PubMed - indexed for MEDLINE]
- 5: Philpot EE, Brooker AE, Biegalski CS.
Effects of sedating and nonsedating antihistamines on flying performance.
Mil Med. 1993 Oct;158(10):654-60.
PMID: 8264923 [PubMed - indexed for MEDLINE]
- 6: Grant JA, Bernstein DI, Buckley CE, Chu T, Fox RW, Rocklin RE, Schoenwetter WF, Spector SL, Stafford CT, Stroh JE Jr, et al.
Double-blind comparison of terfenadine, chlorpheniramine, and placebo in the treatment of chronic idiopathic urticaria.
J Allergy Clin Immunol. 1988 Mar;81(3):574-9.
PMID: 3126220 [PubMed - indexed for MEDLINE]
- 7: Gaffey MJ, Gwaltney JM Jr, Sastre A, Dressler WE, Sorrentino JV, Hayden FG.
Intranasally and orally administered antihistamine treatment of experimental rhinovirus colds.
Am Rev Respir Dis. 1987 Sep;136(3):556-60.
PMID: 3307567 [PubMed - indexed for MEDLINE]
- 8: Rumore MM, Schlichting DA.
Clinical efficacy of antihistaminics as analgesics.
Pain. 1986 Apr;25(1):7-22.
PMID: 2872645 [PubMed - indexed for MEDLINE]
- 9: von Maur K.
Antihistamine selection in patients with allergic rhinitis.
Ann Allergy. 1985 Sep;55(3):458-62.
PMID: 2864005 [PubMed - indexed for MEDLINE]

10: Long WF, Taylor RJ, Wagner CJ, Leavengood DC, Nelson HS.
Skin test suppression by antihistamines and the development of subsensitivity.
J Allergy Clin Immunol. 1985 Jul;76(1):113-7.
PMID: 4008809 [PubMed - indexed for MEDLINE]

11: Cook TJ, MacQueen DM, Wittig HJ, Thornby JI, Lantos RL, Virtue CM.
Degree and duration of skin test suppression and side effects with
antihistamines. A double blind controlled study with five antihistamines.
J Allergy Clin Immunol. 1973 Feb;51(2):71-7. No abstract available.
PMID: 4405284 [PubMed - indexed for MEDLINE]

12: Aschan G.
Habituation to repeated rotatory stimuli (cupulometry) and the effect of
antinausea drugs and alcohol on the results.
Acta Otolaryngol. 1967 Aug;64(2):95-106. No abstract available.
PMID: 4861759 [PubMed - indexed for MEDLINE]

Appendix 2

Previous review from CD-ROM E:\BRIEFING_NOTES\FORMATTED\antiallergics.doc

1. Chlorpheniramine (with square box listing)

Licensing status in children:

UK: Syrup not licensed for children under 1 year; tablets not licensed for use in children under 6 years; injection not licensed for use in neonates. Tablets indicated for use in allergy, injection for treatment of anaphylaxis (not in neonates).

Australia, US: not licensed for use in children (Cranswick review).

In Australia, dexchlorpheniramine is used (dextroisomer of chlorpheniramine) where oral liquid is used in children aged 2-6 years and tablets used in children 6-12 years for the treatment of allergic conditions (e.g. rhinitis, conjunctivitis, urticaria, contact dermatitis), pruritus and adjunctive treatment for anaphylactic and anaphylactoid reactions (AMH January 2007).

Specific safety issues in relation to use in children:

BNF-C (2006): Suggests sedating antihistamines should not be given to children under 2 years except on specialist advice, because safety of use has not been established. In addition, sedating antihistamines have significant anti-muscarinic activity and should not be used in neonates, and should be used with caution in children with urinary retention, glaucoma or pyloroduodenal obstruction.

Route of administration, appropriateness of dose form and strength:

BNF-C (2006) suggests usual doses in children under 12 years for symptomatic relief of allergy such as hayfever and urticaria are 1mg twice daily (1 month-2 years), 1 mg 4-6 hourly (children 2-6 years) and 2 mg every 4-6 hours (children 6-12 years). Therefore if chlorpheniramine is considered appropriate in children, there may be a need for a liquid formulation (2 mg/5 ml).

Current listing in 15th EML:

Injection: 10 mg (hydrogen maleate) in 1-ml ampoule.

Tablet: 4 mg (hydrogen maleate).

Other comments received on listing of this medicine:

FIP: Have deleted chlorpheniramine and suggested that diphenhydramine injection 50 mg/ml and tablets 25 mg be added to the Model List.

HW Seyberth (German perspective): Comments that chlorpheniramine appears popular in the UK but is unknown in Germany, apart from use in a combination flu

medication. Notes that if the additional sedative effect of an older antihistamine is appreciated, dimetindene (Fenestil) is of widespread use on the Continent for decades, licensed for children >1 year and available in most age appropriate formulations including droplets. Otherwise, cetirizidine is preferred antiallergic agent. Provides some more recent references for dimetindene.

Appendix 3

WHO Technical Report Series

Section 3. Antiallergics and medicines used in anaphylaxis

The current listing in the 15th EML includes

3. **Antiallergics and medicines used in anaphylaxis:** chlorphenamine, dexamethasone, epinephrine, hydrocortisone, prednisolone.

Reviews of this Section were prepared by Dr Coelho and Dr Peterson. Comments were received as listed in Annex 6. No applications for additional medicines for this Section were submitted. The Subcommittee considered that allergic disorders (e.g. rhinitis, conjunctivitis, urticaria and contact dermatitis) are a common problem in children and therefore medicines for their treatment could be considered essential. Epinephrine was endorsed as essential for treatment of anaphylaxis. The question of inclusion of antihistamines was more difficult. The value of sedating versus non-sedating antihistamines needs to be assessed, and there are national preferences for particular medicines within these classes. Different dosage forms need to be available, and it was noted that if, for example, oral liquid forms of antihistamines were recommended, these might not be appropriate for use in children under 2 years. In the absence of a formal review of comparative effectiveness and safety, the Subcommittee decided to endorse the inclusion of chlorphenamine injection and tablets with a square box on the Model List, noting that the choice of medicine within the class of sedating antihistamines would be a national one, depending upon availability and cost. The Subcommittee recommended that these medicines be reviewed as chlorphenamine is not registered for children under 1 year of age and may not be the best indicative drug for this class. The Subcommittee requested a review of diphenhydramine to assess the comparative efficacy and safety with chlorphenamine, as it may be applicable to a broader age range of children than chlorphenamine. It also noted the need for a review of the use of non-sedating antihistamines in children for its next meeting.