Medicines Classification Committee

Meeting date	1 May 2017	58th Meeting	
Title	**Reclassification of Sedating Antihistamines**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For decision
Proposal for reclassification to prescription medicine for some indications	The Medicines Adverse Reactions Committee (MARC) recommended that the committee consider reclassifying sedating antihistamines to prescription medicines when used in children under 6 years of age for the treatment of nausea and vomiting and travel sickness [exact wording to be determined by the committee].		
Reason for submission	The purpose of this document is to provide the committee with an overview of the information provided to the MARC about safety concerns associated with sedating antihistamines and reasons for recommendations.		
Associated *Prescriber Update* articles	March 2013	Children and Sedating Antihistamines	
	February 2010	Cough and cold medicines clarification – antihistamines	
	Medsafe website	Safety information: Use of cough and cold medicines in children – new advice	
Medicines for consideration	Alimemazine Brompheniramine Chlorpheniramine Cyclizine Dexchlorpheniramine	Diphenhydramine Doxylamine Meclozine Promethazine	
New Zealand exposure to sedating antihistamines		Some oral sedating antihistamines available without a prescription (pharmacist-only and pharmacy only), therefore usage data is not easily available.	

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1.0 PURPOSE

At the 166th meeting of the Medicines Adverse Reactions Committee (MARC) the Committee recommended that the Medicines Classification Committee (MCC) consider reclassifying all sedating antihistamines when used in children under 6 years of age for the treatment of nausea and vomiting and travel sickness to prescription medicines. This will not change the classification for use in allergic conditions (ie, will still be available as a pharmacist only medicine for the treatment of allergic conditions in children aged 2 years of age and older).

The purpose of this document is to provide the MCC with information about the safety of sedating antihistamines and the reasons for the MARC recommendations for reclassification consideration.

Although overall there would still be different age categories for use, dependent upon the indication, this would apply to all oral sedating antihistamines to reduce confusion. A summary of the proposed changes is as follows:

Summary table*:

Indication	**Age**
Allergic conditions (includes hayfever, allergic reactions)	Pharmacist only medicine for adults and children 2 years of age and older.
Nausea and vomiting	Prescription medicine for use in children 2 to 5 years of age (under 6 years old); pharmacy only medicine for adults and children 6 years and older
Travel sickness	Prescription medicine for use in children 2 to 5 years of age (under 6 years old); pharmacy only medicine for adults and children 6 years and older
Insomnia	Contraindicated in children younger than 12 years of age; pharmacist only medicine for adults and children 12 years of age and older.
Cough and cold	Contraindicated in children younger than 6 years of age; pharmacy only medicine for adults and children 6 years of age and older.

*All sedating antihistamines contraindicated in children less than 2 years of age.

2.0 BACKGROUND

Sedating antihistamines are used for a number of indications, although not all sedating antihistamines are approved for all indications. The range of indications include:

- a night time sleep aid for the short-term management of insomnia
- the treatment of allergic conditions including some allergic reactions to drugs, urticarial and allergic contact dermatitis, and allergic reactions to insect bites and stings
- the relief of excessive secretion in the upper respiratory tract as a result of hayfever and allergic rhinitis
- an anti-emetic for vomiting from various causes including post-operative vomiting, irradiation sickness, drug-induced nausea and motion sickness
- the relief of vomiting and attacks of vertigo associated with Meniere's disease and other forms of vestibular disturbance

- a premedication for anaesthesia
- the relief of runny nose, sneezing, itching of nose or throat, itchy watery eyes due to cold or flu (ie, in cough and cold medicines)

The main difference between first (sedating) and second (non-sedating) generation antihistamines is that sedating antihistamines readily cross the blood-brain barrier. Non-sedating antihistamines are highly specific for H1-receptors, are large lipophilic molecules, are extensively albumin-bound, and have little to no anticholinergic, antiserotonergic or anti-alpha-adrenergic effects. Consequently, there are fewer associated adverse reactions with non-sedating antihistamines. The cholinergic activity of first generation antihistamines causes symptoms of drowsiness and reduced concentration, as well as dry mouth, blurry vision and urinary retention[1]. One of the main concerns with using sedating antihistamines in children is the risk of sedation and respiratory depression.

As first generation antihistamines were introduced from 1942 until the mid-1980s, there is a paucity of information relating to potency, efficacy and safety. There are six structural classes of antihistamines, of which both first and second generation antihistamines are included (Table 1). Although characteristic pharmacological properties have been described for each structural class, many of the effects of antihistamines vary from patient to patient[2].

Table 1: Structural classes of H1 antihistamines[2]

Alkylamines (propylamines)	Ethanolamines	Ethylenediamines	Phenothiazines	Piperidine	Piperazines
First generation					
Brompheniramine Chlorpheniramine Dexchlorpheniramine Pheniramine Triprolidine	Clemastine Diphenhydramine Doxylamine	Antazoline Mepyramine	Promethazine Trimeprazine	Azatadine Cyproheptadine	Buclizine Cyclizine Hydroxyzine Mebhydrolin Meclizine
Second generation					
Acrivastine				Astemizole Desloratadine Ebastine Fexofenadine Levocabastine Loratadine Mizolastine Terfenadine	Cetirizine Levocetirizine

The efficacy of different H1 antihistamines in the treatment of allergic patients is similar, even when comparing first and second generation antihistamines. However, they are different in terms of chemical structure, pharmacology and toxic potential (although this is also difficult to determine with a lack of study information).

[1] Gonzalez MA, Estes KS. Pharmacokinetic overview of oral second-generation H1 antihistamines. *International Journal of Clinical Pharmacology and Therapeutics* 1998; 36(5): 292–300.
[2] Van Schoor J. Antihistamines: a brief review. *Prof Nurs Today* 2012; 16(5): 16-21

2.1 Other Information and Recommendations from the 166th MARC meeting

The MARC considered that the data available indicates that restricting use by age and/or indication is appropriate. See section 4 and 5 below for information on the scientific information including published data and Centre for Adverse Reactions Monitoring (CARM) data.

In addition to the change in classification to prescription only recommendation for the treatment of nausea and vomiting and travel sickness in children under 6 years of age, the MARC also recommended that:

- all sedating antihistamines should be contraindicated in children under 2 years of age (for all indications).
- the use of sedating antihistamines for the treatment of cough and colds should remain contraindicated in children under 6 years of age.
- the use of sedating antihistamines for the treatment of insomnia should be contraindicated in children under 12 years of age.
- the Label Statements Database (LSD) be updated to remove 'anxiety' as a condition for labelling requirements.
- the LSD be updated to reflect other changes. LSD consultation will occur following the MCC meeting.

The purpose of these recommendations is to align all sedating antihistamines so that depending on the indication(s) for use and classification there will be clear age restrictions. As noted above there are a variety of indications for use of sedating antihistamines, which complicates this issue.

The resulting changes would be as follows:

- all sedating antihistamines are contraindicated in children under 2 years of age for all indications.
- all sedating antihistamines are contraindicated in children under 12 years of age for the treatment of insomnia (should insomnia be an indication for use).
- all sedating antihistamines remain contraindicated in children under 6 years of age for the treatment of coughs and colds (cough and cold medicines containing sedating antihistamines are currently classified as pharmacy-only medicines; this will not change).
- **all sedating antihistamines are prescription-only medicines when used in children under 6 years of age for treatment of nausea and vomiting and travel sickness (remain available as pharmacist-only medicines for these indications in children 6 years and older) – for MCC discussion; MARC recommendation**
- all sedating antihistamines indicated for treatment of allergic conditions are pharmacist-only medicines for use in children 2 years and older (must be appropriately labelled with dosing instructions for allergic conditions only in the 2-5 year old age group).

Comments:

Should a particular sedating antihistamine be already approved for an indication with an age restriction or classification that is higher than these recommendations, then the approval will not change. These changes apply only to products where the age restriction is not clear or is lower than recommended and will also need to be considered when future approvals are given to sedating antihistamine-containing products.

2.2 Previous Cough and Cold Review Group and Medicines Classification Committee Information

Comments:

Please note, the original query that prompted the MARC review of sedating antihistamines was in relation to dexchlorpheniramine (brand Polaramine). Therefore, some of the information below specifically relates to this medicine. The below information also provides a timeline for some of the differences in classification and restrictions on age of use of different sedating antihistamines.

The Cough and Cold Review Group (CCRG) reviewed the benefits and risk of using cough and cold medicines in children in 2009. The CCRG recommended that cough and cold medicines be contraindicated for use in children under six years of age (with the exception of nasal sprays and bromhexine – although bromhexine was reviewed at the 160th MARC meeting [December 2014] and has now been updated in the LSD to align with other cough and cold medicines).

Sedating antihistamines with an indication for symptoms of cough and cold were included in this recommendation (brompheniramine, chlorphenamine [chlorpheniramine], diphenhydramine, doxylamine, promethazine and triprolidine). Dexchlorpheniramine was not included in this review, presumably because there were no products containing dexchlorpheniramine indicated for symptoms of cough and cold.

At the 44th meeting of the MCC in November 2010 a potential confusion was discussed that was a consequence of the recommendations of the CCRG. At the time, sedating antihistamines were classified as pharmacy-only medicines when **combined** with one or more therapeutically active ingredients for the treatment of coughs, colds or influenza when at least one of the other active ingredients is a sympathomimetic decongestant or in a day/night pack containing the sedating antihistamine in the bedtime dose and in preparations for adults and children over **two** years of age. This contradicted the recommendation to contraindicate use of cough and cold medicines in children under **six** years of age.

Dexchlorpheniramine was considered to be affected by this recommendation even though it was not included in the initial cough and cold review. It was recommended that **all** sedating antihistamines should then be classified as pharmacy-only medicines when in **combination** for adults and children over **six** years of age (contraindicated in children under six years of age).

For other indications sedating antihistamines are classified as restricted/pharmacist-only medicines or prescription medicines. The use of sedating antihistamines for allergy was not considered by the CCRG and was not affected by the above recommendations.

It was also noted at the 44th MCC meeting that at a previous meeting Medsafe had been asked to review the labelling of **all** sedating antihistamine products to ensure that these were contraindicated in children under two years of age and that there was a warning statement about use with other cough and cold medicines (from the 38th MCC meeting).

Comments:

The recommendation that sedating antihistamines are classified as pharmacy-only when in combination as specified above in adults and children over six years of age was adopted. The recommendation from a previous MCC meeting to review the labelling of all sedating antihistamine products to ensure that they were contraindicated in children under two years of age (for any indication) does not appear to have been implemented.

*This may be because the 38th MCC meeting minutes and recommendations differ slightly – within the body of the minutes it is noted that Medsafe should be asked to review the labelling of all **combination** packs to ensure that the products were contraindicated in children under the age of two and in the recommendations section it is noted that Medsafe should be asked to review the labelling of **all** sedating antihistamine products (single ingredient or combination). When this issue was considered at the 44th MCC meeting (November 2010), all combination products had already been contraindicated in children less than two years of age, as this was the recommendation in the text.*

At the time of the 38th MCC meeting (December 2007) a report had also been prepared for the MARC. The MARC report reviewed the safety and efficacy of cough and cold medicines, which may include sedating antihistamines, available for use in children, not the use of sedating antihistamines for any other indications.

It cannot be determined from the minutes where the labelling review changed from all combination packs to all sedating antihistamine products or if this was the actual intention.

2.3 Database of Medicines Classifications

The conditions listed below are applicable to many sedating antihistamines including alimemazine (trimeprazine), brompheniramine, chlorpheniramine, dexchlorpheniramine, doxylamine and promethazine. Some of these sedating antihistamine products have a higher lower age limit for use than is recommended in the database of medicines classifications (eg, chlorphenamine (Histafen brand)) has a lower limit of six years of age for the prescription medicine product – see also Table 2 on data sheet information below).

- **Prescription** – except when specified elsewhere in this schedule
- **Restricted** – for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units
- **Pharmacy Only** – for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing dexchlorpheniramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant

Comments

In summary, dexchlorpheniramine (amongst other sedating antihistamines) is a:

- *prescription medicine if used in children under two years of age for any indication and when used in children under six years of age in combination products for cough and cold*
- *restricted medicine (pharmacist only) when used in patients over two years of age for indications other than insomnia and anxiety (eg, allergy) or for use in insomnia and anxiety in packs not more than 10 dosage units*
- *pharmacy only medicine when used in combination in patients over six years of age for cough and cold symptoms*

The lower age restriction of two years is included in the database of medicines classifications for restricted medicines (except in the treatment of anxiety or insomnia). This age restriction would therefore apply to use in other indications, such as allergy, when not on prescription.

The reasons for including some indications for use in the database of medicine classifications rather than the LSD is not apparent. The conditions for classification has led to the confusion around the lower age limit for use.

This classification change was gazetted in January 2012. When the LSD was established, there was a review undertaken to check that all of the requirements from the New Zealand Regulatory Guidelines for Medicines were either in the LSD or Schedule 1 (list of medicines in the Medicines Regulations 1984). Sedating antihistamines were initially overlooked and this gazette notice was to include the Restricted Medicines information in Schedule 1, Part 2. It is not known how this age restriction and indication classification was decided upon and came to be included in Schedule 1 as there is no further information about whether a review of the labelling was undertaken.

Other sedating antihistamines such as cyclizine, meclozine, mepyramine, pheniramine and ketotifen have different classifications due to formulation differences (eg, eye drops, cream) or other restrictions (eg, insomnia or anxiety indication).

3.0 DATA SHEET INFORMATION

The following table summarises information about sedating antihistamines, including indications, contraindications and classification. The classification and indications of each sedating antihistamine has some determination on the age group in which the product can be used in (as already noted in 2.3 Database of Medicines Classification).

The different indications, classifications, contraindications and consequently different ages for use are confusing and inconsistent, which is the main reason for the MCC submission. Information from Canada, the UK, Australia and the USA is also included to compare information in different countries.

Table 2: Indications, contraindications and classification of different sedating antihistamines

Please note that some pharmacy only medicines have data sheets although this is not a requirement. It is only a requirement for prescription medicines and restricted (pharmacist only) medicines to have an accompanying data sheet.

Antihistamine	Current Classification	Indications	Contraindications and Warnings
Alimemazine (Trimeprazine)	Prescription medicine	Urticaria and pruritus Premedication for anaesthesia	Children less than 2 years of age
Brompheniramine	Varied depending on indication; only available in combination with decongestant so pharmacy only medicine	No data sheet available as pharmacy only medicine – for the treatment of the common cold	Children less than 6 years of age as in combination product; children 6 to 11 years only on the advice of a doctor, pharmacist or nurse prescriber (package labelling only)
Chlorphenamine (Chlorpheniramine)	Varied depending on indication; available in both combination products and single ingredient product	Prescription (single ingredient) product – allergic skin disorders and seasonal and perennial allergic rhinitis No data sheet for combination products (pharmacy only medicine)	Prescription product - Do not use in children under six years of age Combination product - Children less than 12 years of age (package labelling only)
Cyclizine	Restricted medicine (less than 10 dosage units, for use other than treatment of anxiety or insomnia), otherwise prescription medicine	Nausea and vomiting cause by motion sickness, vertigo, narcotic analgesics and general anaesthetics	Not recommended in children under 6 years of age
Dexchlorpheniramine	Varied depending on indication; single ingredient product so restricted medicine	Perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, urticaria and angioedema	Not to be used in children under 2 years of age
Diphenhydramine	Varied depending on indication; available as combination product or single ingredient product for sleep so restricted medicine	Single ingredient - sleep aid for short-term management of insomnia Combination product - temporary relief of pain when associated with sleeping difficulty	Do not give to children under 12 years of age
Doxylamine	Restricted medicine; available as a combination product or single ingredient product	Single ingredient - temporary use in the relief of insomnia	Not recommended for children under 12 years of age

		Combination product - symptomatic relief of acute moderate to severe pain; tension headache and migraine	Children (aged below 18 years) who undergo tonsillectomy and/or adenoidectomy – due to codeine component in combination product
Ketotifen*	Varied depending on indication; only available as eye drops so pharmacy only medicine	Treatment and prevention of signs and symptoms of seasonal allergic conjunctivitis	Dosage instructions for children aged 3 years and above only
Meclozine	Pharmacy only medicine	No data sheet available as pharmacy only medicine – relief of travel sickness	Do not give to children under 6 years of age (package labelling only)
Mepyramine*	General sale medicine; only available as topical cream	Symptomatic relief in insect stings and bites and nettle rash	No age limit for use
Pheniramine*	Varied depending on indication; only available in combination as eye drops so pharmacy only medicine	Symptomatic treatment of allergic conjunctivitis	Safety and effectiveness in children under 12 years of age have not been established (not a contraindication or warning)
Promethazine	Varied depending on indication; pharmacy only medicine and restricted medicine	Pharmacy only - prevention and treatment of motion sickness Restricted - treatment of allergic conditions, excessive secretion in the upper respiratory tract, anti-emetic, sedation	Should not be used in children less than ten years of age (pharmacy only) Should not be used in children less than two years of age (restricted) – dosage and administration section; children under 2 years of age – contraindications section

***As ketotifen, mepyramine and pheniramine are not available in New Zealand in an oral formulation, they are not included in the remainder of this review**

Canada product information

Table 3: Indications, contraindications and classification of different sedating antihistamines (Canada)

Antihistamine	Current Classification	Indications and Age of use (where available)	Contraindications and Warnings
Trimeprazine	Prescription only	Pruritus regardless of site or aetiology. Cough of various aetiologies.	Trimeprazine is contraindicated for use in children less than two years of age. Trimeprazine is contraindicated for use in children less than two years of age due to the risk of marked sedation and respiratory depression.
Brompheniramine (in combination)	OTC or Narcotic (CDSA I; when contains codeine); information not available for all products	When product information available – for temporary relief of coughing and complications of allergic states; symptomatic relief of cough, nasal stuffiness and rhinitis accompanying the common cold. Not recommended in patients below the age of 12 years due to increased safety concerns (due to codeine content).	Product may cause drowsiness or excitability, especially in children.
Chlorpheniramine (single ingredient or in combination)	OTC; information not available for all products	When product information available (combination products only) – temporary relief of symptoms associated with the common cold. Children under 12 years of age should not use or not indicated for children less than 12 years of age.	
Cyclizine	No product information available; cancelled post-market		
Dexchlorpheniramine	No product information available; cancelled post-market		
Diphenhydramine (single ingredient or in combination)	OTC; information not available for all products	When product information available (combination products only) – for the relief of cold and influenza symptoms.	

		Not indicated for children less than 16 years of age.	
Doxylamine (single ingredient or in combination)	OTC or Narcotic (CDSA I; when contains codeine); information not available for all products	Single ingredient – night-time sleep aid. Combination product (when product information available) – relief of headaches, cold symptoms, muscular acnes and pains	Not recommended for children under 12 years of age.
Meclozine	Product not found in search		
Promethazine	OTC or Narcotic (CDSA I; when contains codeine); information only available for injectable form		

UK product information

Table 4: Indications, contraindications and classification of different sedating antihistamines (UK)

Antihistamine	Current Classification	Indications and Age of use (where available)	Contraindications and Warnings
Trimeprazine	Prescription only	For management of urticaria and pruritus. Pre-medication as a sedative before anaesthesia in children aged between 2 to 7 years.	Alimemazine is contraindicated for use in children less than 2 years of age. Alimemazine is contraindicated for use in children less than 2 years of age due to the risk of marked sedation and respiratory depression
Brompheniramine	Product not found in search		
Chlorpheniramine (single ingredient or in combination)	Most products available OTC	For symptomatic relief of hayfever, vasomotor rhinitis, urticaria, angioneurotic oedema, reactions to food or medicines, serum reactions and insect bites. Children under 1 year: Not recommended (liquid; single ingredient). Not recommended for children under the age of 6 years (tablet; single ingredient).	Contraindications – Not recommended for children under 2 years (combination). Premature infants or neonates because of their increased susceptibility to the antimuscarinic effects (liquid; single ingredient).

			Warnings and Precautions – Consult a pharmacist of other healthcare professional before use in children under 6 years (combination).
Cyclizine	OTC and prescription	Prevention and treatment of nausea and vomiting, including motion sickness, nausea and vomiting caused by narcotic analgesics and anaesthetics, and vomiting associated with radiotherapy.	Do not give this medicine to children under the age of 6.
Dexchlorpheniramine	Product not found in search		
Diphenhydramine (single ingredient or in combination)	OTC	Relief of cough and associated congestive symptoms. Symptoms associated with colds and influenza. Do not give to children under 16 years (tablet or liquid for sleep; single ingredient). Do not give to children under 12 years old (liquid for cough; combination), or not recommended for children under 12 years of age except on medicine advice (tablet for night time pain/sleep; combination).	Do not give to children under 12 years old (liquid for cough; combination), or contraindicated in premature infants or neonates who have increased susceptibility to antimuscarinic effects (tablet for night time pain/sleep; combination).
Doxylamine	Product not found in search		
Meclozine	Product not found in search		
Promethazine (single ingredient or in combination)	OTC and prescription	Symptomatic treatment for allergic conditions. Relief of colds, chills and influenza symptoms (combination product). Not for use in children under the age of 2 years.	Contraindicated for use in children less than two years of age because of the potential for fatal respiratory depression.

Australia product information

Table 5: Summary of TGA information relating to use of sedating antihistamines in children

Antihistamine	Current Classification	Indication	Contraindications and Warnings
Trimeprazine	Prescription only	Urticaria – treatment of pruritus irrespective of the cause.	Alimemazine is contraindicated for use in children less than 2 years of age. Alimemazine is contraindicated for use in children less than 2 years of age due to the risk of marked sedation and respiratory depression.
Brompheniramine	OTC; no product information available		
Chlorpheniramine	OTC; no product information available		
Cyclizine	Product information only for injection		
Dexchlorpheniramine	OTC; no product information available		
Diphenhydramine	OTC; No product information available		
Doxylamine (in combination)	Prescription only	For relief of severe pain not responding to milder analgesics.	Contraindicated in patients younger than 12 years and patients aged between 12-18 years in whom respiratory function might be compromised.
Meclozine	Product not found in search		
Promethazine	OTC: product information only for injection		

US product information

Table 6: Summary of FDA information relating to use of sedating antihistamines in children

Antihistamine	Current Classification	Indication and Age of use (where available)	Contraindications and Warnings
Trimeprazine	Discontinued; no product information available		

Brompheniramine (single ingredient or in combination)	OTC and prescription (both single ingredient and combination)	Temporarily relieves cough due to minor throat and bronchial irritation occurring with a cold, and nasal congestion due to the common cold, hayfever and other upper respiratory allergies. Do not use in children under 6 years of age.	Do not use to make a child sleepy
Chlorpheniramine (single ingredient or in combination)	OTC	Do not use in children under 12 years of age (combination). Do not use in children under 6 years of age (single ingredient).	
Cyclizine	OTC and prescription	For the prevention and treatment of the nausea, vomiting or dizziness association with motion sickness. Children under 6 years of age: Consult a physician	
Dexchlorpheniramine (single ingredient or in combination)	OTC	Temporarily relieves these symptoms (runny nose, sneezing, itching of nose or throat, itchy or water eyes, nasal congestion and reduces swelling of nasal passages) due to the common cold, hayfever or other respiratory allergies. Children under 6 years of age: Consult a doctor	
Diphenhydramine	OTC	Temporarily relieves these symptoms (runny nose, sneezing, itching of nose or throat, itchy or water eyes, nasal congestion and reduces swelling of nasal passages) due to the common cold, hayfever or other respiratory allergies. Do not use this product in children under 6 years of age.	

Doxylamine (single ingredient or in combination)	OTC	Helps to reduce difficulty in falling asleep (single ingredient). Do not use in children under 12 years of age. Temporarily relieves common cold/flu symptoms (cough due to minor throat and bronchial irritation, sore throat, headache, minor aches and pains, fever, runny nose and sneezing) (combination). Children under 4 years, do not use; children 4 to under 12 years, ask a doctor.	
Meclozine	No product information available		
Promethazine (single ingredient and combination)	OTC and prescription	For allergic rhinitis, pre and postoperative sedation, and prevention and control of nausea and vomiting with certain types of anaesthesia, motion sickness and postoperative (single ingredient). Temporary relief of coughs and upper respiratory symptoms, including nasal congestion, associated with allergy or the common cold (combination).	Contraindicated for use in paediatric patients less than two years of age. Should not be used in paediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Postmarketing cases of respiratory depression, including fatalities, have been reported with use of Promethazine in paediatric patients less than 2 years of age. A wide range of weight-base doses of Promethazine have resulted in respiratory depression in these patients. Cause should be exercised when administering Promethazine to paediatric patients 2 years of age and older. It is recommended that the lowest effective dose of Promethazine be used in paediatric patients 2 years of age and older and concomitant administration of other drugs with respiratory depressant effects be avoided.

4.0 PUBLISHED LITERATURE

As part of the MARC review, Medsafe performed a review of the literature. However, as sedating antihistamines have been available for many years, there is limited information about first generation antihistamines and use in children. There is even less evidence to support the use of sedating antihistamines for relief of nausea and vomiting and travel sickness. Additionally, there are other medicines, particularly for the relief of nausea and vomiting, available that have a more favourable side effect profile.

The following summarises available evidence provided to the MARC for the use of sedating antihistamines in different indications in children as well as information about the risk of respiratory depression with sedating antihistamines. Not all of the studies provided to the MARC are included in this submission, as not all studies are relevant.

4.1 Prevention and treatment of motion sickness – Brainard and Gresham (2014)[3]

This summary paper describes the symptoms of motion sickness and interventions to prevent or minimise symptoms.

The use of scopolamine is recommended as a first-line medicine for preventing motion sickness in persons who wish to maintain wakefulness during travel, with an evidence rating of 'A' (consistent, good quality patient-oriented evidence).

The recommendation for first generation antihistamines as effective for preventing motion sickness, but often having sedative and other side effects is an evidence rating of 'B' (inconsistent or limited quality patient-oriented evidence).

The following outlines different antihistamines medicines for motion sickness (columns include medicines, effectiveness for prevention and dose.

Antihistamines (first-generation, listed from least to most sedating)		
Cinnarizine[15]	Moderately effective	Adults and children older than 12 years: 30 mg two hours before travel, then 15 mg every eight hours as needed Children five to 12 years of age: 15 mg two hours before travel, then 7.5 to 15 mg every eight hours as needed
Cyclizine (Marezine)[17]	Least effective	Adults and children older than 12 years: 50 mg one hour before travel, then every four to six hours as needed (maximum: 200 mg per day) Children six to 11 years of age: 25 mg one hour before travel, then every six to eight hours as needed (maximum: 75 mg per day)
Dimenhydrinate[16,18]	Least effective	Adults and children older than 12 years: 50 to 100 mg every four to six hours (maximum: 400 mg per day) Children six to 12 years of age: 25 to 50 mg every six to eight hours as needed (maximum: 150 mg per day)
Diphenhydramine	Least effective	Adults and children older than 12 years: 25 to 50 mg every four to six hours (maximum: 300 mg per day) Children six to 12 years of age: 12.5 to 25 mg every four to six hours as needed (maximum: 150 mg per day)
Promethazine[16,19]	Moderately effective	Adults: 25 mg 30 to 60 minutes before travel, then every 12 hours as needed Children: 12.5 to 25 mg twice daily as needed
Meclizine (Antivert)[16,18]	Least effective	Adults and children 12 years and older: 25 to 50 mg one hour before travel, then every 24 hours as needed Children younger than 12 years: not recommended

[3] Brainard A and Gresham C. Prevention and Treatment of Motion Sickness. *Am Fam Physician* 2014; 90 (1): 41-46

The only moderately effective antihistamines that is available in New Zealand, promethazine, is one of the most sedating of the first generation antihistamines.

Cyclizine, dimenhydrinate, promethazine and meclozine demonstrated effectiveness in small randomised controlled trials of varying quality.

4.2 Antihistamines for the common cold – De Sutter et al. (2015)[4]

The objective of this Cochrane review was to assess the effects of antihistamines on the common cold. The authors searched CENTRAL (2015, Issue 6), MEDLINE (1948 to July week 4, 2015), EMBASE (2010 to August 2015), CINAHL (1981 to August 2015), LILACS (1982 to August 2015) and Biosis Previews (1985 to August 2015).

Randomised controlled trials (RCTs) using antihistamines as monotherapy for the common cold were selected. Any studies with combination therapy or using antihistamines in patients with an allergic component in their illness were excluded. Adverse effects information from the included trials was collected.

A total of 18 RCTs were included, with 4342 participants (of which 212 were children) suffering from the common cold, both naturally occurring and experimentally induced. The interventions consisted of an antihistamine as monotherapy compared with placebo. Thirteen trials used a sedating antihistamine as the intervention, the most common of which was chlorpheniramine maleate in five trials followed by clemastine fumarate in three trials. The remaining sedating antihistamines were brompheniramine maleate, doxylamine succinate, and diphenylpyraline.

In adults there was a short-term beneficial effect of antihistamines on severity of overall symptoms: on day one or two of treatment 45% had a beneficial effect with antihistamines versus 38% with placebo (odds ratio (OR) 0.74, 95% confidence interval (CI) 0.60 to 0.92). However, there was no difference between antihistamines and placebo in the mid-term (three to four days) to long term (six to 10 days).

When evaluating individual symptoms such as nasal congestion, rhinorrhoea and sneezing, there was some beneficial effect of the sedating antihistamines compared to placebo (eg, rhinorrhoea on day three: mean difference (MD) -0.23, 95% CI -0.39 to -0.06 on a four- or five-point severity scale; sneezing on day three: MD - 0.35, 95% CI -0.49 to -0.20 on a four-point severity scale), but this effect is clinically non-significant. Adverse events such as sedation were more commonly reported with sedating antihistamines although the differences were not statistically significant.

Only two trials included children and the results were conflicting. Hugenin (1988) studied the effect of astemizole on cold symptoms in 62 children from the age of two to 15 years. Inclusion criteria were watery or mucous rhinorrhoea, cough and malaise. A major problem with this trial was the long duration of symptoms before inclusion (mean six days, ranging from one to 365). Some children obviously did not have a common cold. The number of days until normalisation of general conditions was 5.2 (± 2.3) with placebo and 4 (± 2.12) with active treatment (P value = 0.06). The number of days until rhinorrhoea severity score was reduced to 50% of initial value with astemizole was 3.4 (± 1.7) and with placebo was 5.1 (± 2) (P value = 0.001). The proportion of children with complete disappearance of rhinorrhoea after 7 days of treatment with astemizole was 79% (18/23) and with placebo was 46% (12/27) (P value = 0.015).

In the trial by Sakchainanont (1990), the effect of clemastine (N = 48) and chlorpheniramine (N = 48) was compared with placebo (N = 47) in children younger than five years of age with rhinorrhoea for three days. The amount of discharge was less after three days with clemastine in 28/48 children, with chlorpheniramine in 25/48 and with placebo in 22/47 (P value = 0.53).

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[4] De Sutter AI, Saraswat A, van Driel ML. Antihistamines for the common cold. *Cochrane Database Syst Rev* 2015 Nov 29; 11: CD009345

The majority of all trials had a low risk of bias although some lacked sufficient trial quality information. The lack of evidence of the effectiveness of antihistamine use in children and the lack of trials investigating use in cough and colds indicates that there is insufficient evidence to support the use of antihistamines for colds in children.

Authors' conclusions

- Antihistamines have a limited short-term (days one and two of treatment) beneficial effect on severity of overall symptoms but not in the mid to long term.
- There is no clinically significant effect on nasal obstruction, rhinorrhoea or sneezing.
- Although side effects are more common with sedating antihistamines, the difference is not statistically significant. There is no evidence of effectiveness of antihistamines in children.

Comments

This review shows that there is a lack of evidence for the use of antihistamines in children for cough and cold symptoms. This reinforces the recommendation to contraindicate use of sedating antihistamines for cough and cold symptoms in children less than six years of age.

Other Cochrane reviews, which considered the efficacy of antihistamines in both acute and chronic cough, found similar results. There was uncertain efficacy for both types of cough and antihistamines cannot be recommended as empirical therapy for children with chronic cough.

The use of antihistamines in children with non-specific cough has to be balanced against the well-known risk of adverse events, especially in very young children.

4.3 Safety considerations in the management of allergic diseases: focus on antihistamines – Yanai et al (2012)[5]

A systematic review was conducted to determine the evidence supporting the safety profiles of frequently used oral H1 antihistamines for the treatment of allergic diseases and to compare them to other medications, mostly topical corticosteroids and leukotriene antagonists.

First generation antihistamines inhibit the effects of histamine not only peripherally but also in the brain, and additionally have potent antimuscarinic, anti-alpha-adrenergic and antiserotonin effects. This leads to symptoms such as visual disturbances (mydriasis, photophobia and diplopia), dry mouth, tachycardia, constipation, urinary retention, agitation and confusion. The somnolence caused by first generation oral antihistamines interferes with the natural circadian sleep-wake cycle and are therefore not suitable to be used as an aid for sleeping.

Second generation antihistamines have better safety and tolerability profiles, much lower proportional impairment rations, with at least similar if not better efficacy.

Authors' conclusion

Only second generation antihistamines should be prescribed for young children. Second generation oral antihistamines are the preferred first-line treatment option for allergic rhinitis and urticaria. Patients taking second generation antihistamines report relatively little and mild adverse events even after long-term continuous treatments.

[5] Yanai K, Rogala B, Chugh K et al. Safety considerations in the management of allergic diseases: focus on antihistamines. *Curr Med Res Opin* 2012 28(4): 632-642

Comments

This review did not provide a large amount of information with regards to first generation antihistamines, most likely as there is not much information available. It does, however, conclude that the efficacy is similar and using second generation antihistamines where adverse events tend to be less pronounced is better for treatment of allergic conditions in young children.

4.4 Use of antihistamines in paediatrics – del Cuvillo et al (2007)[6]

This review provided an update on antihistamine use in children, though first generation antihistamines have never been adequately studied for paediatric age groups. As a result, the authors recommended that these should not be recommended as first line treatment.

All first generation antihistamines are metabolised in the liver by the P450 cytochrome enzyme system. There are no studies of the effects of possible drug interactions in paediatric age groups between antihistamines and P450 cytochrome inhibitors, or drugs that are metabolised via this pathway. The only exception is a study by Okonkwo et al. (2006) of children with chloroquine-resistant malaria, where the plasma concentrations of this medicine were seen to be significantly greater, and were reached sooner, when administered in combination with chlorpheniramine.

A study by Munday et al. (2002) concluded that chlorpheniramine was no more effective than placebo in ameliorating the symptoms of childhood atopic dermatitis with nocturnal itching and scratch marks, and that antihistamine use does not affect the amount of topical treatment used over the short term.

Table 7 shows the most important pharmacological aspects according to the studies published on the antihistamines most widely used in paediatrics.

[6] del Cuvillo A, Sastre J, Montoro J et al. Use of antihistamines in paediatrics. *J Investig Allergol Clin Immunol* 2007; 17 S2: 28-40

Table 7: Pharmacological characteristics of antihistamines most commonly used in paediatric patients

Drug	Dose (mg or mg/kg*)	Patients (no.)	Age (years)	Cp max (ng/ml)	Tmax (h)	$T_{1/2}$ (h)	erythema/wheal (h)
First generation							
Brompheniramine	4	14	9.5 ± 0.4	7.7 ± 0.7	3.2 ±0.3	12.4 ± 1.1	0.5 to 36
Chlorpheniramine	0.12*	11	11 ± 3	13.5 ± 3.5	2.5 ± 1.5	13.1 ± 6.3	1 to 24
Diphenhydramine	1.25*	7	8.9 ± 1.7	81.8 ± 30.2	1.3 ± 0.5	5.4 ± 1.8	1 to 12
Hydroxyzine	0.7*	12	6.1 ± 4.6	47.4 ± 17.3	2.0 ± 0.9	7.1 ± 2.3	n/d
Ketotifen	1 (c/12h)	6	3 ± 1	3.25	1.33	n/d	n/d
Second generation							
Cetirizine	5	10	8 ± 0.6	427.6 ± 144.2	1.4 ± 1.1	7.1 ± 1.6	1 to 24
	10	9	8 ± 0.6	978.4 ± 340.6	0.8 ± 0.4	6.9 ± 1.6	0.5 to 24
	5	8	2.7	560 ± 200	1.44 ± 1.1	4.9 ± 0.6	n/d
	0.25	15	12.3 ± 5.5m	390 ± 135	2 ± 1.3	3.1 ± 1.8	90% at 12 h
Ebastine	5	10	7.3 ± 0.4	108.6 ± 11.8	2.8 ± 0.3	11.4 ± 0.7	0.5 to 28
	10	7.8 ± 0.4	209.6 ± 24.2	3.4 ± 0.4	10.1 ± 1.1	0.5 a 28	
Fexofenadine	30 (c/12 h)	14	9.8 ± 1.8	178 ± 22	2.4 ± 0.2	18.3 ± 1.2	1 to 24
	60 (c/12h)	14	9.8 ± 1.8	286 ± 34	2.4 ± 0.2	17.6 ± 1	1 to 24
Loratadine	10	13	10.6	4.38	1	13.79	1 to 12
	5	18	3.8 ± 1.1	7.8	1.2	n/d	n/d
Levocetirizine	0.125* (c/12h)	15	20.7 ± 3.7m	286 ± 68	1	4.1 ± 0.67	1 to 28
	0.18*	14	8.6 ± 0.4	450 ± 37	1.2 ± 0.2	5.7 ± 0.2	n/d
Desloratadine	N 183 (76.3%)	58	>6m-<1				
	1.25		1-2				

No studies of the required methodological quality have been conducted in children with urticaria of any origin to determine the efficacy of antihistamines.

Few data have been published on the role of antihistamines in the treatment of anaphylaxis in children. A study by Fan et al. (1999) found no significant performance of promethazine versus placebo in the prevention of anaphylaxis following snake bite in South America. In a review of idiopathic anaphylaxis in children, treatment including hydroxyzine and ketotifen was successful in improving patient response to corticosteroids (adrenaline was always on hand).

The evidence for the efficacy of sedating antihistamines in cough is also limited. A meta-analysis by Chang et al. (2006) found that brompheniramine in combination with decongestants was no superior to placebo for acute cough in children, while Schroeder and Fahey (2004) determined that antihistamines alone (clemastine and chlorpheniramine) also afforded no greater benefit than placebo.

Many of the antihistamine indications in children have been based on the extrapolation of the effects of these medicines in adults. Calculation of paediatric dose has been done with little or no pharmacokinetic data corresponding to the different paediatric age groups.

Few studies have explicitly investigated the effect of first generation antihistamines upon the CNS in children, though some data have been obtained from comparative studies contrasting the different generation antihistamines.

Simons et al. (1996) assessed diphenhydramine and hydroxyzine for effects upon cognitive processes and drowsiness in children with allergic rhinitis. The study concluded that both medicines induce objective dysfunctions at CNS level, and drowsiness. Another study, also by Simons et al. (1994), concluded that neither terfenadine nor placebo induced cognitive changes, in contrast to chlorpheniramine.

A study by Ng et al. (2004) in 24 children between seven and 14 years of age diagnosed with allergic rhinitis, found that both chlorpheniramine and cetirizine induced significant cognitive alterations versus placebo. However, such alterations were not correlated to subjective appraisal of dysfunction as assessed by means of a visual analog scale.

Reports of rare adverse effects in children administered first generation antihistamines include spasms, seizures, aggression, respiratory distress, fixed skin rash, central anticholinergic syndrome and toxic encephalopathy in patients with skin syndromes involving damage to the skin barrier (where the first generation antihistamines were applied topically). Both deaths and serious toxicity have been documented in paediatric patients' treated with first generation antihistamines.

Authors' conclusion

Non-cardiotoxic second generation antihistamines are the medicines of choice for the recommended treatment indications, for patients of all ages. First generation antihistamines should be held in reserve for infrequent situations where their adverse effects may prove desirable, or when parenteral dosing is required. Further research is needed to warrant the different indications and further define aspects such as the dosage and the treatment regimen best suited to each individual.

Comments

This review shows that there is minimal evidence for the safety and efficacy of first generation antihistamines for a number of different indications.

4.5 Safety and tolerability of treatments for allergic rhinitis in children – Baena-Cagnani (2004)[7]

This review discussed the safety and tolerability of treatment for paediatric allergic rhinitis, including oral antihistamines. However, only the second generation antihistamines were included (loratadine, cetirizine and fexofenadine). With regards to sedating antihistamines, the following was discussed:

'First generation H1 antihistamines, although effective in relieving the symptoms of rhinitis and urticaria, are associated with unwanted adverse effects, such as sedation and impairment of psychomotor function, due to a lack of H1 receptor selectivity, and, in particular, their penetration into the CNS.

Few studies have assessed the incidence of adverse effects of first generation antihistamines in children. However, reports of severe adverse reactions and deaths following overdoses of first generation antihistamines in paediatric patients have been published. Despite the lack of adequate studies in children and infants, many of the old sedating antihistamines are still commonly given to this population.'

Whilst sedating antihistamines were not formally included in this review, limited information was discussed.

Tachycardia - Older generation antihistamines were associated with adverse effects, including dry mouth and urinary retention, as a result of blockade of muscarinic cholinergic receptors. The H1 receptor shares close sequence homology with the muscarinic M1 to M5 receptors. Studies have shown that the M1 receptor has a role in memory function and is located in the CNS and ganglia, whereas the M3 receptor is located on glandular and smooth muscle cells. The M2 subtype is involved in maintaining vagal tone and blockade of this receptor and is linked with tachycardia. In vitro binding studies have led to a great understanding of the cardiac effects of different

[7] Baena-Cagnani CE. Safety and tolerability of treatments for allergic rhinitis in children. *Drug Saf* 2004 27(12): 883-898

antihistamines and have shown that this activity is separate from H1 antihistaminic potency and is, therefore, not class-related.

Sedation and impairment – Histamine has been widely reported to play an important role in maintaining CNS arousal and alertness. Therefore, antihistamines that cross the blood-brain barrier and antagonise H1 receptors in the brain can produce impairment of cognitive function, including attention, memory, sensorimotor coordination, information processing and psychomotor performance. In infants and young children, stimulatory effects of first-generation H1 antihistamines on the CNS have also been shown to result in irritability, nervousness, hyperactivity and seizures. Data from studies using first generation antihistamines demonstrated significant adverse effects as a result of their sedative properties, producing impairment of cognitive and academic function in children.

The rigorous testing of antihistamines to ensure the CNS safety of these agents is a relatively recent development. Penetration into the CNS in adults can be measured objectively using psychometric tests. In children, a lack of adverse effects from second generation H1 antihistamines has been demonstrated using EEG and psychomotor performance tests. A study of the effects of antihistamines on childrens' learning ability demonstrated that the first generation antihistamine diphenhydramine caused significantly more learning impairment compared with loratadine.

Comments

This review does not specifically include first generation antihistamines, but occasionally compares their adverse effects with the newer second generation antihistamines. This review shows that there is a general lack of information about the first generation antihistamines and there are concerns about sedation, impairment and possibly tachycardia.

4.6 Antihistamines, respiratory depression and the sudden infant death syndrome in young children – a review and recommendations – Scolnik and Koren (1996)[8]

Three WHO reports caution against the use of histamine antagonists in infants due to fear of respiratory depression possibly leading to sleep apnoea and sudden infant death syndrome (SIDS) – the first warning that administration to children less than one year old may be associated with episodes of sleep apnoea and that products containing a phenothiazine antihistamines should be formally contraindicated for this reason, except on medical advice; the second from Zyma Inc that it had deleted recommendations for the use of the antihistamine dimetindene syrup and drops in infants; the third from the FDA that all preparations containing promethazine should be subjected to prescription control because of the associations with both SIDS and neurological effects.

The objectives of this study were to review the evidence pertaining to these recommendations and to define which antihistamines (if any) should be included in such recommendations.

Ethanolamines (eg, diphenhydramine and doxylamine) and phenothiazines (eg, promethazine and alimemazine) have a marked sedative effects, whereas alkylamines (eg, chlorpheniramine and brompheniramine) and piperazines (eg, hydroxyzine) have mild to moderate, dose-related, sedating effects. Additionally, phenothiazines have α-adrenergic blocking activity, which may cause hypotension.

Kahn and Blum reported a link between the treatment of upper respiratory tract infections with promethazine and alimemazine and SIDS in 1979 and 1982. The presence of upper respiratory tract symptoms during the prior week and drug administration during the previous two days were

[8] Scolnik D and Koren G. Antihistamines, respiratory depression and the sudden infant death syndrome in young children – a review and recommendations. *Can J Clin Pharmacol* 1996 3(2); 71-74

recorded. The incidence of nasopharyngitis was similar in the SIDS group, the 'near-miss' group and control group. The use of the liquid form of phenothiazine drugs was significantly higher in the SIDS victims. A further study showed a decrease in number of arousals and gross body movements, a 39% increase in sleep apnoeas and occurrence of obstructive sleep apnoea when the infants' sleep was evaluated with and without a dose of promethazine.

Walker and Romieu (1988) determined that promethazine can induce sleep apnoeas in normal infants, that sleep apnoeas in infancy may be causally linked to at least some cases of SIDS and that drugs that affect central respiratory control in infancy must be considered as potential risk factors for SIDS (although no drugs found in the infants in this study played a role in the epidemiology of SIDS). It was concluded that promethazine is a far less significant risk factor for SIDS than other known factors.

Authors' conclusions

- Phenothiazine-type antihistamines have been shown to induce sleep apnoeas in young children
- Phenothiazine-type antihistamines have been associated with near SIDS and SIDS
- Phenothiazine- and ethanolamine-type antihistamines are substantially more sedating than other types of antihistamines
- Published studies have neither implicated nor vindicated antihistamines, other than those of the phenothiazine-type, in causing sleep apnoea in infants or young children.

Comments

This study indicates that the phenothiazine-type antihistamines are more sedating and more likely associated with sleep apnoea than other antihistamines groups. It does not exclude other sedating antihistamines from being associated with sleep apnoea. This review is 20 years old; there is minimal additional evidence to confirm these conclusions.

4.7 Night-time sedating H1-antihistamine increases daytime somnolence but not treatment efficacy in chronic spontaneous urticaria: a randomised controlled trial – Staevska et al. (2014)[9]

In this randomised, double-blind, cross-over study, 24 patients with difficult to treat chronic spontaneous urticaria took levocetirizine (15 mg daily) plus hydroxyzine (50 mg at night) or levocetirizine monotherapy (20 mg daily) for periods of five days each. At the end of each treatment period, assessment were made of quality of life, severity of urticaria symptoms (Urticaria Activity Score – UAS), sleep disturbance during the night and daytime somnolence.

Both treatments significantly decreased UAS, night-time sleep disturbances and increased quality of life scores, without significant differences between the two. Compared with baseline, daytime somnolence was significantly reduced by levocetirizine monotherapy (P = 0.006) but not by levocetirizine plus hydroxyzine (P = 0.218). Direct comparison of the two treatment modalities in terms of daytime somnolence favoured levocetirizine monotherapy (P = 0.026) (see Figure 1).

[9] Staevska M, Gugutkova M, Lazarova C et al. Night-time sedating H1-antihistamine increases daytime somnolence but not treatment efficacy in chronic spontaneous urticaria: a randomised controlled trial. *Br J Dermatol* 2014 171 (1): 148-154

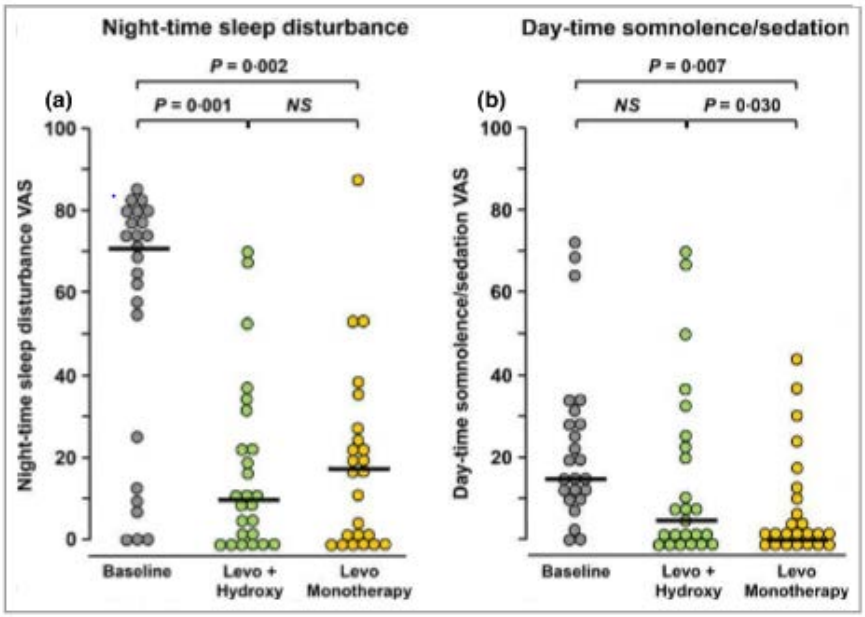

Figure 1: Visual analogue scores for night-time sleep disturbance and daytime sedation at the start of the study (baseline) and after 5 days of treatment

Authors' conclusion

The widespread belief that sleep is aided by the addition of a sedating first generation H1-antihistamine at night is not supported. These results are in line with the urticaria guidelines, which state that first-line treatment for urticaria should be new generation, non-sedating H1-antihistamines only.

Comments

This study shows that second generation antihistamines are effective in reducing urticaria, and that first generation antihistamines do not improve sleep, but instead increase the risk of daytime somnolence.

4.8 Adverse central nervous system effects of older antihistamines in children – Simons et al. (1996)[10]

The CNS effects of first generation antihistamines have not been well-documented in young subjects. The authors hypothesized that diphenhydramine and hydroxyzine would affect CNS function adversely in this population. The objective was to evaluate the effects of these medications on central and peripheral histamine H1-receptors in children. Fifteen subjects with allergic rhinitis were tested before and 2-2.5 hours after administration of diphenhydramine, hydroxyzine, or placebo in a double-blind, single-dose, three-way crossover study.

Impairment of cognitive processing was assessed objectively by the latency of the P300 event-related potential (P300). Somnolence was assessed subjectively by a visual analogue scale. Peripheral H1-blockade was assessed by suppression of the histamine-induced wheals and flares. At the central (Cz) and frontal (Fz) electrodes, diphenhydramine and hydroxyzine increased the P300 latency significantly ($P < 0.05$) compared to baseline. Hydroxyzine increased somnolence, as

[10] Simons, FER, Fraser TG, Reggin JD et al. Adverse central nervous system effects of older antihistamines in children. *Pediatr Allergy Immunol* 1996 7 (1): 22-27

recorded on the visual analogue scale, significantly compared to baseline ($P < 0.05$), with a similar trend for diphenhydramine ($P = 0.07$).

Both antihistamines reduced histamine-induced wheals and flares significantly compared to baseline and compared to placebo.

Authors' conclusion

In children, diphenhydramine and hydroxyzine are effective H1-receptor antagonists, but both these medications cause CNS dysfunction, as evidenced by increased P300 latency, a measure of cognitive function, and by increased subjective somnolence.

Comments

This study shows that while first generation antihistamines may be effective in allergic conditions, they also contribute to CNS dysfunction.

4.9 Literature Comments

Other studies/reviews not included in this paper, indicated that there is very little evidence to support the use of sedating antihistamines for anxiety disorders.

Case reports show instances of poisonings and overdosage when sedating antihistamines were used in children.

Whilst there is evidence to support the use of sedating antihistamines for allergic conditions, the evidence for use in treating nausea and vomiting, motion sickness and insomnia is less apparent.

There is the risk of sedation, respiratory distress and CNS dysfunction with the use of sedating antihistamines particularly in young children, which is the reason for the MARC recommendation to reclassify the use of all sedating antihistamines in children less than six years of age for the nausea and vomiting and travel sickness indications to prescription medicines (will align with the cough and cold age restriction).

5.0 CARM DATA

The Centre for Adverse Reactions Monitoring (CARM) has received 23 reports of adverse reactions associated with sedating antihistamines in children under six years of age. These date from January 1967 through until November 2011.

Of these reports, seven listed trimeprazine (alimemazine), five listed ketotifen, three listed cyclizine, two each with promethazine, Dimetapp and cetirizine (considered to be a non-sedating or second generation antihistamines, though may cause sedation in a small percentage of users), and one each with meclozine and the combination of trimeprazine, prochlorperazine and cyclizine.

The reported reactions varied, although there were reports of somnolence, confusion, cyanosis, dyspnoea, apnoea and coma included in the cohort.

6.0 CONCLUSION

The oral sedating antihistamines include alimemazine (trimepramine), brompheniramine, chlorphenamine (chlorpheniramine), dexchlorpheniramine, diphenhydramine, doxylamine, meclozine and promethazine.

There are different age restrictions for use for the different sedating antihistamines, due to the different indications for use and different formulations. Information in the label statements database and the database of medicines classifications adds further confusion to requirements and

age limits for use. For example, a minimum of two years of age for use applies to sedating antihistamines when not on prescription according to the database of medicines classifications.

There is a paucity of information about the safety and efficacy of sedating or first generation antihistamines. Where efficacy information is available it tends to show that they are similar to non-sedating or second generation antihistamines for allergic reactions and that there is little evidence supporting their use for symptoms of coughs and colds, and use as sleeping aids. Where safety information is available it tends to show that they are more likely to be associated with sedation, confusion, and possibly sleep apnoea and tachycardia.

One study indicated that phenothiazine-type antihistamines maybe more likely to be sedating and associated with sleep apnoea than other antihistamines, but this does not exclude other sedating antihistamines types from these adverse effects.

The MARC have made other recommendations including contraindicating all sedating antihistamines in children under 2 years of age for all indications due to the risk of adverse effects and under 12 years of age for the insomnia indication. These changes will be reflected in the LSD and are under consultation. Additionally, 'anxiety' will be removed as a condition (indication) for labelling, as there is little evidence to support the use of sedating antihistamines for anxiety and the reasoning for including this indication in the LSD is not known.

The contraindication for use in children less than six years of age for cough and cold symptoms is to remain. As noted, respiratory depression is the main concern with sedating antihistamines and if treatment is for symptoms that include lower respiratory tract infection this may increase the risk of adverse events.

Although overall there would still be different age categories for use, dependent upon the indication, this would apply to all sedating antihistamines to reduce confusion.

Summary table*:

Indication	**Age**
Allergic conditions (includes hayfever, allergic reactions)	Pharmacist only medicine for adults and children 2 years of age and older.
Nausea and vomiting	Prescription medicine for use in children 2 to 5 years of age (under 6 years old); pharmacy only medicine for adults and children 6 years and older
Travel sickness	Prescription medicine for use in children 2 to 5 years of age (under 6 years old); pharmacy only medicine for adults and children 6 years and older
Insomnia	Contraindicated in children younger than 12 years of age; pharmacist only medicine for adults and children 12 years of age and older.
Cough and cold	Contraindicated in children younger than 6 years of age; pharmacy only medicine for adults and children 6 years of age and older.

*All sedating antihistamines contraindicated in children less than 2 years of age.

The MCC is asked to consider reclassifying sedating antihistamines to prescription only medicines when used in children under 6 years of age for the indications of nausea and vomiting, and travel sickness, with the exact wording to be determined by the committee.

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