Reviewer No. 1 Section 3

ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS

For proposed ‘yellows’: Are these medicines for children?

Do these medicines meet a public health?

Chlorphenamine: Yes.

Do these medicines meet a public health?
Yes. Chlorphenamine

Are they registered for use in (all age categories of) children?
No.

Chlorphenamine maleate oral:
Doses for children are: 1 to 2 years, 1mg twice daily; 2 to 5 years, 1mg every 4 to 6 hours (maximum 6 mg daily); 6 to 12 years, 2mg every 4 to 6 hours (maximum 12 mg daily).
Martindale 33 ed., P.412

Chlorphenamine maleate oral:
Children < 12 year oral: 0.35mg/kg/day in divided doses every 4-6 hours or as an alternative 2 to 5 years: 1mg every 4 to 6 hours
6 to 11 years, 2mg every 4 to 6 hours, not to exceed 12mg/day or timed release 8mg every 12 hours.
Chlorphenamine maleate I.M., I.V., S.C.;
Children < 12 years: 0.0875mg/kg or 2.5 mg/m² 4 times / day

Are there any anaswered/unexpected clinical issues with respect to effectives or safety?
No.

Additional comments if any:
Único medicamento antialérgico existente na lista com dados sobre utilização em crianças, devendo ter atenção especial ao efeito adverso da palpitação.


Registro Cochrane de Ensaios Controlados (CENTRAL/CCTR)
Loratadine and dexchlorpheniramine in the treatment of perennial allergic rhinitis in pediatric patients
Effect of allergy medication on children's reading comprehension.
Efficacy and safety of loratadine suspension in the treatment of children with allergic rhinitis.
Comparative study of the efficacy, tolerance and side-effects of dexchlorpheniramine maleate 6 mg b.i.d. with terfenadine 60 mg b.i.d.
Comparison of CNS adverse effects between astemizole and chlorpheniramine in children: a randomized, double-blind study.

Anaphylaxis

Patients with severe anaphylactic or anaphylactoid reactions should be given immediate treatment with adrenaline (see Anaphylaxis and Anaphylactic Shock, Adrenaline Hydrochloride). Addition of a parenteral antihistamine such as chlorphenamine maleate or diphenhydramine hydrochloride and a corticosteroid such as hydrocortisone after the acute episode may decrease the duration and severity of symptoms and prevent relapse.

MARTINDALE - The Complete Drug Reference acesso em 28/05/2007

Indications and dose

**Symptomatic relief of allergy such as hay fever, urticaria**

By mouth

- Child 1 month–2 years
  - 1 mg twice daily
- Child 2–6 years
  - 1 mg every 4–6 hours, max. 6 mg daily
- Child 6–12 years
  - 2 mg every 4–6 hours, max. 12 mg daily
- Child 12–18 years
  - 4 mg every 4–6 hours, max. 24 mg daily

**Symptomatic relief of allergy, emergency treatment of anaphylactic reactions**

By subcutaneous, intramuscular or intravenous injection

- Child 1 month–1 year
  - 250 micrograms/kg (max. 2.5 mg), repeated if required up to 4 times in 24 hours
- Child 1–6 years
  - 2.5–5 mg, repeated if required up to 4 times in 24 hours
Child 6–12 years
5–10 mg, repeated if required up to 4 times in 24 hours

Child 12–18 years
10–20 mg, repeated if required up to 4 times in 24 hours (max. 40 mg in 24 hours)

NOTE
Intravenous route recommended for anaphylaxis; subcutaneous and intramuscular injections rarely act quicker than oral administration

Licensed use
syrup not licensed for use in children under 1 year; tablets not licensed for use in children under 6 years; injection not licensed for use in neonates

Administration

*for intravenous injection*, give over 1 minute; if small dose required, dilute with Sodium Chloride 0.9%

Antihistamines should be used with caution in hepatic impairment, and the dose may need to be reduced in renal impairment; also, use with caution in children with epilepsy. Most antihistamines should be avoided in porphyria, but some (e.g. chlorphenamine) are thought to be safe. Sedating antihistamines should not be given to children under 2 years, except on specialist advice, because the safety of such use has not been established. Sedating antihistamines have significant antimuscarinic activity—they should **not** be used in neonates and should be used with caution in children with urinary retention, glaucoma, or pyloroduodenal obstruction.

Hepatic impairment

Sedating antihistamines should be avoided in children with severe liver disease—increased risk of coma.

Side-effects

Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely in children, especially with high doses. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines (see also notes above). Side-effects that are more common with the older antihistamines include headache, psychomotor impairment, and antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastro-intestinal disturbances. Other rare side-effects of antihistamines include hypotension, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, palpitation, arrhythmias, hypersensitivity reactions (including bronchospasm, angioedema, anaphylaxis, rashes, and photosensitivity reactions), blood disorders, and liver dysfunction.

Side-effects

Also exfoliative dermatitis and tinnitus reported; injections may cause transient hypotension or CNS stimulation and may be irritant

For ‘greens’: Is there any reason not to endorse these as essential medicines for children?

Dexamethasone

Do these medicines meet a public health? Yes

Are they registered for use in (all age categories of) children? Yes

Neonates: I.V. Usual: 0.25mg/kg/dose given ~ 4 hours prior to scheduled extubation and then every 8 hours for 3 doses total; range: 0.25-1 mg/kg/dose for 1-3 doses; maximum dose 1mg/kg/day.

Children: I.V., I.M: 0,5 - 2mg/kg/dose in divided doses every 6 hours; begin 24 hours prior to extubation and continue for 4-6 doses after extubation.


Are they any unanswered/unexpected clinical issues with respect to effectiveness or safety? No

Are there special requirements or training needed for safe/effective use? No.

Additional comments if any:

Action proposed for the Committee to take:
PERGUNTA AOS PEDIATRAS: É NECESSÁRIO DEXAMETAZONA PARA USO EM ANAFILAXIA, ALERGIAS?

Epinephrine

Do these medicines meet a public health? Yes

Are they registered for use in (all age categories of) children? Yes

- The dose of epinephrine should be 0.01 mg/kg, up to a maximum of 0.30 mg. This presents a dilemma for clinicians in that the prefilled autoinjector kits use doses of only 0.15 and 0.30 mg/ kg, making the precise dosing of children and adolescents difficult if not impossible. While there is little direct evidence comparing one dose with another, the authors suggest the following dosing algorithm based on patient weight:
  - 10 kg or less: Consider use of ampule of epinephrine with needle and syringe to draw correct dose (0.01 mg/kg) of epinephrine. The main difficulties with this approach are timing and accuracy. One study demonstrated that parents required 142 seconds to draw a dose of 0.09 mL of epinephrine vs 52 seconds for clinicians. Moreover, the actual dose of epinephrine drawn by parents ranged between 0.004 and 0.151 mL.
  - 10 to 25 kg: Autoinjection with 0.15 mg of epinephrine.
  - 25 kg or more: Autoinjection with 0.30 mg of epinephrine.
- A second dose of epinephrine is required for anaphylaxis in up to 35% of cases. Epinephrine may be repeated 5 to 20 minutes after the initial dose.
- Brasil: (RENAME) somente sol injetável 1mg/ml
Are they any unanswered/unexpected clinical issues with respect to effectiveness or safety? “No”.

The risk is well known. A necessidade de fazer uma diluição muito grande é um risco.

Are there special requirements or training needed for safe/effective use?

Yes; careful dilution procedure

Possible transient adverse events associated with epinephrine administration include tremor, anxiety, and palpitations.

Epinephrine should be kept away from extreme temperatures and direct sunlight to protect against drug degradation, and the solution will not necessarily appear different after degradation has occurred.

Martindale 33 ed., P.829

The injection with the EpiPen, every child developed transient pallor, tremor, anxiety, and palpitations or other cardiovascular effects; some also developed headache and nausea.


Martindale 33 ed., P.829

Additional comments if any: In many countries there is only one concentration marketed

Action proposed for the Committee to take: to approve; to suggest other dilutions; prefilled siringues

For ‘greens ‘: Is there any reason not to endorse these as essential medicines for children?

Hydrocortisone

Do these medicines meet a public health? Yes

Are they registered for use in (all age categories of) children? Yes

Children: Initial: 50mg/kg then repeated in 4 hours and/or every 24 hours if needed


Children up to 1 year of age may be given 25mg, those aged 1 to 5 years 50 mg, and those aged 6 to 12 years 100mg.

Martindale 33 ed., P.1074

Pediatric Min/Max Dose: 0.16mg/kg/50.0mg/kg

Are they any unanswered/unexpected clinical issues with respect to effectiveness or safety? No.

Are there special requirements or training needed for safe/effective use? No
Additional comments if any:

Action proposed for the Committee to take:
PERGUNTAMOS AOS PEDIATRAS: ESTE MEDICAMENTO É NECESSÁRIO NESTA CATEGORIA?

For proposed ‘yellows’: Are these medicines for children?

**Prednisolone**

Do these medicines meet a public health? Yes.

Are they registered for use in (all age categories of) children? Yes

**Prednisolone Oral**
Some clinicians state that children may be given a prednisolone dosage of 0.14–2 mg/kg daily or 4–60 mg/m² daily, administered in 4 divided doses.

**Prednisolone Sodium Phosphate Oral (better taste)**
Pediatric Min/Max Dose: 0.1mg/kg/2.0mg/kg

**Methylprednisolone Acetate Injectable Suspension USP**
Intramuscular, 0.14 to 0.84 mg per kg of body weight or 4.16 to 25 mg per square meter of body surface area every twelve to twenty-four hours.
USP Expert Committees consensus on review of the ballot, 01/2002.

Are there any unanswered/ unexpected clinical issues with respect to effectives or safety?
No.

Additional comments if any:
Use of preparations containing benzyl alcohol is not recommended in neonates. A fatal toxic syndrome consisting of metabolic acidosis, central nervous system (CNS) depression, respiratory problems, renal failure, hypotension, and possibly seizures and intracranial hemorrhages has been associated with this use.

USP Expert Committees consensus on review of the ballot, 01/2002.

Prelone® syroup contains benzoic acid and Orapred® oral solution contains sodium benzoate; use with caution in neonates, as these preservatives may displace bilirubin from protein binding sites and at larges doses can cause the gasping syndrome.