Position paper on preferred dosage forms to be included in a Model Essential Medicines List for Children

Introduction

The report on the 4th Model List of Essential Drugs includes guidelines for the selection of pharmaceutical dosage forms.[1] Under the heading of "criteria for the selection of essential drugs", the report states that "each selected drug must be available in a form in which adequate quality, including bioavailability, can be assured". Other issues identified were "stability under anticipated conditions of storage and use", the relative cost of different dosage forms, "general utility" and "wide availability internationally". Unfortunately, the report states, "Specific paediatric dosages and formulations are included in the list only when indicated by special circumstances".

The purposes of these policy statements are to:

1. Identify which factors should be taken into account when making a choice of paediatric dosage forms to be included in a Model Essential Medicines List for Children.
2. Review the evidence for the suitability of different formulations for paediatric medicines, considering such factors as have been identified, including issues of dosing accuracy, palatability, stability, ease of transport and storage.
3. Recommend preferable formulations for different age groups of children, including neonates premature & full term , young infants and older children.

These policy statements are primarily extrapolated from clinical practice and available published information including the European Medicine Agency Committee for medicinal products for Human use, reflection paper: Formulation of choice for the paediatric population, dated 28 July 2006.

Overarching statement

Liquid formulations can offer superior palatability to dissolved-solid tablets, intended for swallowing whole, however the transportation, storage and temperature monitoring required for liquid formulations render this bulky dosage form as a potential barrier for their use in regions of the world under stress or harsh living conditions.

Policy statement: The stability of and having access to paediatric medicines is paramount. Whenever possible, every effort must be extended to optimize their palatability of paediatric medicines . The ideal paediatric formulation characteristics listed below are desirable when the chemical stability or product availability allows. When the stability or product availability does not permit one of the following suggested characteristics, this should not prevent pediatric patients from accessing medications.

[1] World Health Organization. The use of essential drugs. Second report of the WHO Expert Committee. Technical Report Series 722, 1985.

Policy statement: Formulations should contain only excipients known to be safe for all paediatric age groups. This is to ensure flexibility in medication supply.

Oral formulations

Policy statement: The preferred oral formulation is the tablet as it is the most easily stored and is stable over the widest range of environmental conditions. Appropriately formulated oral Tablets (see below) can meet the needs of most paediatric patients when used properly in providing point of care, as patient specific solutions, suspensions or slurries can be prepared at the time of administration. Chewing gum, capsules, oral powder, orodispersible and oromucosal dosage formulations are acceptable, but require age-specific dosage forms. In the absence of an ability to modify the dose amount for these latter dose forms (e.g., cutting the patch formulation to a specific dose, etc.) these fixed dose formulations are not practical when considering dosing accuracy, palatability, stability, ease of transport and storage.

Factors to consider in choosing a tablet formulation:

- Tablets should be scored so they may be easy split (with fingers) accurately accommodate a quarter dose.
- Dosages should be standardized using increments of one-quarter tablet for most drugs with a wide therapeutic window. Many doses may be adapted from using a tablet that can be divided in four sections, with a quarter tablet providing a dose for a 10 kg child.
- Tablets should disintegrate easily in water to enable preparation of a point of care, patient specific solutions, suspensions or slurries at the time of administration (e.g., dissolve one-fourth of a tablet in 1.25 to 2.5 mL of water to administer one-eighth of a tablet. This accommodates a medication naïve patient to take a medication by simply mixing it to water prior to administration. In applying such extemporaneous point of care dosing it is highly desirable for calibrated measuring spoons be available and used to ensure dosage accuracy of the specific solution/suspension/slurry at the time of administration.
- Water used to suspend or dilute tablets should be free of contaminants and pathogens.
- Excipients should be inert, gluten free, lactose free and free from dyes that may cause allergic reactions or side effects such as tartrazine and red dyes.
- For patient safety, tablets should be identifiable by different colours or branding imprints or markings. The use of unique imprint code on tablet forms should be mandated.
- Chewable or orally disintegrating tablets are preferred to oral suspensions when a flavour is required to mask bad tasting medication. Chewable or orally disintegrating tablets should disintegrate in water easily to enable the preparation of point of care, patient-specific solutions/suspensions/slurries at the time of administration.
- Slow release formulations should be avoided unless absolutely clinically required or that can be cut or crushed to provide better dosing versatility.

Policy statement: Liquid formulations should be restricted to less palatable medications that prevent children from achieving a therapeutic benefit. Cost effective chewable or orally disintegrating tablets are preferred to oral suspensions/ liquids when a flavour is required to mask bad testing medications. Chewable or orally disintegrating tablets should disintegrate in water easily to enable a point of care, patient specific solutions, suspensions or slurries at the time of administration. Cylindrical measuring spoons or oral dosing syringes should be provided to ensure dosage accuracy when a liquid formulation is dispensed.

Factors to consider in choosing a liquid formulation:

- The dose volume should be ≤ (less than) 5mL for children under 5 years and ≤ (less than) 10mL for children 5 years or older.
- Oral solution (oral drops) of very small dose volumes is acceptable if the manufacturer provides recommendations for dilution in beverage to improve palatability.
- Suspensions should be free of excipient(s) that may cause undesirable effects including diarrhea with sorbitol or xylitol.
- Water used to reconstitute suspensions should be free of contaminants and pathogens.
- Flavours selected should have been shown to effectively mask poor taste without risk of adverse effects.
- Afford very versatile temperature storage range focusing on room temperature & a temperature range that accommodates expected environmental temperatures within the world's many temperent zones.
- Dry powder to be re-constituted at point of care

Parenteral formulations

Factors that should be considered in for parenteral formulations include:

- Preferably use preservative free, single dose or safe preservative –avoid excipient that may be harmful to paediatric patients, e.g., neonates and benzoyl alcohol, propylene glycol. …..
- preference should be given to latex free rubber stopper containers, port of IV tubing and bags;
- formulation should be available in a protected from light containers;
- preferred storage at room temperature;
- tear off label from original vial to label syringes for patient safety.

Injectables

Policy statement: The intravenous and subcutaneous routes are the preferred routes for parenteral administration as are applicable to all age groups.

In choosing an intravenous formulation the following should be considered:

- Manufacturers should provide dilution information to enable to have the medication be administered via central or peripheral vein in children.

- The product should be compatible with glucose 5% &10%, sodium chloride 0.45% and 0.9% and a combination of glucose and saline as well as in the presence of important primary electrolytes, e.g., potassium, chloride, calcium and possibly magnesium.
- The maximum rate of administration should be stated in mg/Kg/minute or microgram/Kg/minute.
- Iso-osmotic and pH neutral preparations are preferred to limit those risks associated with infiltration toxicity, thrombophlebitis and hemolysis.

In choosing a Subcutaneous formulation the following should be considered:

- The medication should be at or near physiological pH of 7.4
- The medication dose should be contained within a small volume.

Policy statement: Intradermal injection should be restricted to medications or tests where there is no other method of administration (e.g., tuberculin test).

Policy statement: Whenever possible, the intramuscular route of drug administration should be avoided. Although undesirable, intramuscular drug administration may be appropriate for a one time dose treatment or in those patients with no venous access and no available surgical expertise for effective line placement. Further, multiple intramuscular doses are problematic from a site stand point and patient tolerability / compliance. In the absence of absolute necessity as noted above, the intramuscular formulation is usually not practical in sick neonates.

Policy statement: Nasal drops, sprays and powders are acceptable dosage form if each are non–irritating and do not affect mucosal function. Penetration enhancers should be shown to be safe and effective in the target population. These formulations may be applicable to all age groups.

Policy statement: Rectal formulations may be applicable in all age groups. However, this mode of administration is not widely accepted by paediatric patients and is thus not preferred unless it is to be used in clinical situations where oral or intravenous administration is not practical (e.g., treatment of nausea and vomiting). The size of the suppository should be related to the patient's size and should be able to split to allow for partial accurate dosages, if necessary.

Policy statement: Topical agents that are commonly used in adults may be used in children of most age groups. However, increased skin surface area and enhanced dermal penetration of infants and neonates must be considered when selecting and dosing topical medications. Transdermal patches should only be used in neonates if there is age specific supporting data available.

Policy statement: Pulmonary agents can be used safely in children; nebulizers may be used in all paediatric age groups but may require specialized equipment. Metered dose inhalers with appropriate age spacers may be used in all age groups except neonates. Dry powder inhalers should be restricted to children greater than 5 years of age.

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20 April 2007

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