Review of Paediatric formulations for the 14th WHO Model Essential Medicine List

Focus on parenteral, inhalational and topical preparations

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Introduction

Over time it has become increasingly clear that there are substantial differences in the absorption, metabolism and excretion of drugs by adults and children. Even *within* the childhood population there are significant differences and changes with time as the child grows and develops. The World Health Organisation (WHO), in collaboration with UNICEF, has prioritised the need to review the Essential Medicines List for children, in particular whether this list appropriately meets the needs of children in the developing world.

Dr Sean Beggs and Dr Noel Cranswick undertook the first stage of this review in 2006. The focus of that review was oral formulations and highlighted numerous drugs on the list that did not have an appropriate formulation for children. With respect to oral medications, the most common issue was that drugs in tablet form were unsuitable for younger children, who are unable to swallow such medications. On the current list, liquid formulations or chewable tables were considered appropriate forms for dosing children but have their limitations.

This review focuses on all other medications on the list – those administered parenterally, topically or via inhalation. Each medication has been reviewed to determine if appropriate for use in children, whether an appropriate formulation is on the list or alternatively, if an appropriate formulation is available in a major international market. For the purposes of this comparison, the international markets included Australia, the United Kingdom and the United States of America.

Background

The need for a paediatric specific medication list.

Children are not small adults. As knowledge of normal growth and development has increased, so has the understanding that developmental changes profoundly affect the

way an individual responds to a medication. It has been well established that there is a need for age-specific dosing of medications and that adjustments must be made as children grow and develop.(1) These age related pharmacodynamic and pharmacokinetic differences also mean that many medications have different effects in children than in adults.(2, 3) It is essential that age-appropriate formulations are available for children of all ages, both to ensure the desired therapeutic effect and minimise any adverse effects.(4)

While there is significant overlap, children, especially newborns, can suffer different diseases to adults. As a result, the medications required to treat these conditions will often differ, creating a need for drug references and formularies specific for the paediatric population. Many countries, such as Australia and the United Kingdom, have addressed this need with paediatric specific and appropriate formularies being readily available.(5, 6)

Formulations

In this review, all medications administered parenterally, topically or via inhalation will be considered. Each of these routes of administration has additional considerations specific to the paediatric population and will be discussed in turn.

Parenteral:

Medications administered via the parenteral route include intravenous, intramuscular and subcutaneous routes.

It is essential that there are suitable intravenous preparations available for children. There is significant variability in the dose of medications required in children, unlike adults, where this is typically quite uniform. Typically doses are based on the weight or body surface area of the child. It must be possible to *accurately* administer small doses of medications to children, however adult preparations may be of a concentration that creates difficulty measuring the dose with reasonable accuracy, or may require multiple dilutions. Every dilution creates an opportunity for an error to be made. In addition, the

process of dilution may introduce pathogens and may affect the safety and efficacy of the drug. When an intravenous preparation is diluted, any preservative is equally diluted which may then be inadequate to retard growth of organisms.(4) Ideally, single use vials should be used wherever possible to eliminate the risk of contamination and/or dosing errors that may be seen if multiple doses are extracted from a single vial. Single use vials, however, are typically more expensive and may not be available in doses appropriate for the paediatric population.(7)

Another important consideration for parenteral administration is with respect to the volume of fluid/medication to be infused or injected. This is particularly significant in the neonatal population, with such a small circulating volume and significant potential for fluid shifts between body compartments. A neonates total daily fluid requirement may be as small as 200-300mls, which can result in significant challenges if requiring multiple medications multiple times a day.

Administrations via the intramuscular or subcutaneous routes also have volume consideration, particularly in smaller children. Of particular consideration is the size/bulk of the muscle injected into, which may be somewhat limiting in any undernourished children. It may be necessary for the required dose to be administered into multiple sites, increasing the subsequent pain and distress for the child. There may also be considerable variation in the absorption of the medication, depending on the site of injection and local perfusion.(7)

Certain parenteral medications are known to have increased toxicity in children compared to adults. These include dopaminergic antagonists, such as metoclopramide or haloperidol, where younger children are at increased risk of acute dystonic reactions or seizures.(8)

<u>Topical – including Ophthalmic and Otic:</u>

Absorption of medication through the skin may be highly variable and significant differences exist between adults and children. The thickness of the skin, which may vary

with anatomical location, hydration and disease state will affect absorption, and is the major rate-limiting factor for topical medications. Young children and neonates in particular have a less developed stratum corneum and therefore 'thinner' skin and increased percutaneous drug absorption. In addition, the increased surface area to body weight ratio in children means that the proportion of drug absorbed per kilogram body weight may be significantly greater. This increases the risk of side effects and systemic toxicity, and is particularly relevant with steroids, retinoids and antibiotics administered topically.(9) The use of iodine-containing solutions for skin preparation must also be carefully considered in very young and premature infants, due to the potential for excess iodine absorption impacting upon thyroid function. Treatment of Scabies in children is another well-recognised situation where there is a significantly increased risk of neurotoxicity in children compared to adults.

Ophthalmic preparations are also more problematic in children compared to adults due to decreased tear volume and excess drug entering the lacrimal system and subsequent absorption systemically. This is particularly relevant with lipophilic drugs, which are readily absorbed by the nasal mucosa, and may result in significant side effects even when used at standard doses.(10) The use of steroid- containing eye drops for children is associated with a significantly increased risk of developing ocular hypertension compared to adults and typically has a more rapid onset. The younger the patient, the higher the risk.(10)

There are additional issues related to administration of ophthalmic preparations in children, who typically find this frightening, leading to increased tears and dilution of any medication, as well as increased risk of local trauma and contamination of administration instrument. The requirement for most ophthalmic preparations to be refrigerated to prolong shelf life and maintain sterility may also be an important consideration in some areas.

<u>Inhalational:</u>

Medications delivered via inhalation on the list include anaesthetic agents and those used for the treatment of asthma. With respect to anaesthetic gases, the dose required is proportional to the lung volume of the child, which is proportional to the weight. As a result, there is no need for differing concentrations for children compared to adults.

The widespread introduction of spacers to facilitate the administration of inhaled bronchodilators and preventers in childhood asthma has improved the efficacy of drug administration and reduced the side effects. Spacer use also minimises the effect of physiological and psychological development on the ability to administer these medications, as spacers of appropriate volume can be used across all age groups. In addition, compared to the use of nebulisers, spacers are inexpensive, portable and do not require an electricity source to function.

Methods

As a review of oral medications on the list has already been undertaken, these were not considered in this review. All other medications on both the core and complementary lists, including parenteral, inhalational and topical formulations, were reviewed.

A medication was considered to be 'indicated' for use in children if it was routinely used to treat the particular condition in children. Treatment for conditions not typically seen in children, such as Parkinson's disease, were deemed not indicated for children.

Drug formularies from three major pharmaceutical markets, being the United Kingdom, Australia and the United States of America, were then examined for each medication, to determine the indications for each drug in children, the preparation available and any relevant licensing restrictions. Consideration was also made as to whether a preparation was 'appropriate' for children, based on its concentration, packaged volume, dilution requirements. If an appropriate formulation was licensed for children, for the given indication, in one of these three major markets, the remaining formularies were not necessarily reviewed.

This information was tabulated in a spreadsheet, with separate sheets for the core and complementary list.

Results

The complete analysis of the list is included in the Data Base in appendix 1.

The core and complementary lists are considered separately here, and summarised in table 1 below.

Core List

Of the 284 medicines on the core list, 121 were not included in the analysis. These were all oral preparations and have been reviewed previously. The remaining 163 medications on the core list were assessed – 142 of these (87%) were judged as indicated for use in children, 13 were not felt to be required in paediatric health care. There were eight medications on the core list that were unable to be adequately assessed and we recommend further consideration of these medications and their role in treating children. For each of these medications, explanatory notes are included in the spreadsheet.

Of the 142 medications on the list indicated for use in children, 132 (93%) were already listed with appropriate formulations, and only 10 (7%) medications indicated for use in children did not already have an appropriate form on the list. For three of those medications, an appropriate paediatric formulation is available in at least one of the sample markets and five were approved for use in children in one of the reference countries.

Complementary List

Of the 84 medications on the complementary list, 30 were oral preparations that have been assessed previously and were therefore excluded. Of the 54 remaining listings, 51 (94%) were judged as requiring a paediatric formulation, with 31 of these already being on the list.

For the 20 medications not currently the list, but requiring a paediatric formulation, five have an appropriate formulation in at least one of the sample markets and two were approved for use in children in one of these markets. The remaining 15 medications on the complementary list were all chemotherapy agents, which were assessed as a group, rather than individually. All were considered indicated for use in children and it is very likely paediatric forms of each of these medications is available but not necessarily approved for use in children, despite their regular use to treat cancer in children. As such, a more accurate statement would be that 45 of the 51 (89%) medications requiring paediatric formulations are already on the current list.

Table 1. Essential Medicine List (14th edition) summary of paediatric formulation(PF) .

	Core	Complementary	Total
Total No of medication listings	**284**	84	**368**
Listings not assessed	**121**	30	**151**
Listings assessed	**163**	54	**217**
PF indicated	**142**	51	**193**
PF not indicated	**13**	0	**13**
"Other"	**8**	**3**	**11**
PF indicated and on the list	**132**	**31**	**163**
PF indicated and not on the list	**10**	**20**	**30**
PF indicated, not on list and available*	**3**	**5**	**8**
PF indicated, not on list and not available*	**7**	**15**	**22**
PF indicated, not on list and approved in ref. country	**5**	**2**	**7**

PF – Paediatric formulation

* In sample markets of Australia, US and UK

Discussion

In stark contrast to the review of oral medications, where almost half of the medications indicated for use in children on the core list were available in one of the sample markets, but not included on the list, the outcome of this review is more positive. On the core list, 93% of parenteral medications indicated for use in children already have an available formulation on the current list. There were only a further three medications indicated for

use in children but without an appropriate formulation on the list, for which an appropriate formulation exists in at least one of the sample markets, and could therefore be included on the Essential Medicines List. Similarly on the complementary list, almost 90% of medications indicated for use in children have an appropriate formulation on the list, with limited scope for improvement.

In its current form, with respect to parenteral/inhalation/topical medications, the Essential Medicines List is adequate and in the vast majority of cases, is responding appropriately to the health needs of children. While these formulations of medications have some important additional considerations when used in children rather than adults, as discussed earlier in this review, there are not the developmental issues, relating to taste and swallowing ability, that are seen when oral preparations are indicated for use in children.

Additional issues related to medication use in children were identified in the process of this review, including 'flagging' specific medications or therapeutic groups for further assessment to improve our ability to provide better healthcare for children in the future.

Recommendations

This review has taken the initial step to improve essential medicines for children, it is recommended that the following be undertaken to continue this improvement;

1. Inclusion of the paediatric formulations on the list that are already commercially available and approved for use in children.
2. Development of guideline to prioritise the medications where a paediatric formulation needs to be developed.
3. Comprehensive review of WHO clinical practice guidelines that apply to children, to identify if medications needed in the treatment of children are *missing* from the EML.
4. Efforts should be focused on improving oral formulations for children to decrease the temptation for the overuse of parenteral formulations and their associated adverse outcomes. Overall in the developing world it is thought that more that 50% of injections occur in an unsafe way, exposing patients to the risk of blood-borne infections(11)

Particular treatment areas identified and recommended for review include:

- African trypsanomiasis
- Severe hypertension in children
- Appropriate intravenous fluids in children
- Chemotherapy
- Agents used for anaesthesia in children

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