Oral Drug Compounding in Children and Availability of Pediatric Formulations: a Canadian Perspective

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Abstract

Background: Despite on-going international efforts**,** many drugs administered to children have no commercially available oral formulations adapted for their needs. This leads to manipulation of dosage forms designed for adults (compounding) which increases the risk of dosing error, exposure to unsafe excipients, and therapeutic failure in children. The scope of this problem is still not well characterized.

Objectives: 1) To describe which drugs required compounding for oral administration for children in Canada; 2) For each compounded drug, to compare regulatory status, and availability of pediatric oral formulations in the United States (US) and European Union (EU).

Methods: We retrospectively identified drugs requiring compounding for oral administration and served to children in a Canadian tertiary pediatric hospital over 1 year (2015-16). Compounding was defined as the preparation of an oral liquid formulation or tablet splitting by the hospital pharmacist. Each drug was classified according to its regulatory status, and availability of commercialized oral formulations in the US and EU. Oral commercially available formulations were deemed adequate, suboptimal or not suitable based on the pharmaceutical form and ingredients described in the product monograph (Table 1).

Results: A total of 89 drugs required compounding. Of those, 78 (88%) were prepared as a liquid formulation, and 18 (20%) required tablet splitting. Of the 57 compounded drugs with no pediatric indication in Canada, 26 (46%) had a pediatric indication in the US or EU. Of the 89 compounded drugs, 20 (22.5%) and 20 (22.5%) had adequate or suboptimal commercially available pediatric formulations, respectively, in the US or EU (Fig 1). A total of 49 (55%) had either an oral form deemed not suitable for children, or no available pediatric formulation.

Conclusion: These results suggest significant variability in the regulatory status of compounded drugs and in access to commercially available pediatric formulations. There is an urgent need for joint guidelines from regulatory agencies to encourage the development of pediatric formulations and facilitate their access to the largest number of children across borders.

Background

- Drug compounding is commonly used to compensate for the lack of oral formulations adapted to children's needs. This practice is essential to provide young children access to medications that are not commercialized in a suitable pharmaceutical form
- Manipulation of dosage forms designed for adults increases the risk of dosing error, exposure to unsafe excipients, and therapeutic failure in children
- The scope of drug compounding is not well characterized

Objectives

- To determine which drugs required compounding for oral administration for children in a tertiary pediatric hospital in Canada over a 1 year period
- To compare regulatory status and availability of commercial pediatric oral formulations in the United States of America (US), and the European Union (EU)

Methods

- We retrospectively identified all drugs requiring compounding for oral administration, and served to children hospitalized at the Centre Hospitalier Universitaire Ste-Justine, Montréal, Canada over 1 year (2015-16)
- Compounding by the hospital pharmacist was defined as either:
  - 1) the preparation of an oral liquid pharmaceutical form by mixing ≥2 ingredients (with at least one being the active pharmaceutical ingredient)
  - 2) tablet splitting
- We excluded drugs compounded due to temporary backorder
- Each drug was classified according to
  - American Hospital Formulary Service Pharmacologic – Therapeutic Classification (AHFS)
  - Regulatory status in Canada, the US, and the EU
  - Availability of commercialized oral formulations in the US and EU
- Oral commercially available formulations were deemed adequate, suboptimal, or not suitable for young children based on the pharmaceutical form and ingredients described in the product monograph (Table 1)

Table 1. Availability of oral pediatric formulation

	Definition
Adequate	Commercialized liquid oral form (solution or suspension) with known safe ingredients
Suboptimal	Commercialized liquid oral form containing one or more ingredients with safety concerns in children (e.g. propylene glycol, sorbitol, phenylalanine) or Commercialized non-liquid adult oral form easily administered to young children, including oral granules, orodispersible tablets, or any oral form requiring manipulation by the parent before administration
Not suitable	Commercialized liquid oral form with ingredients known to be toxic in children (e.g. alcohol)

Results

- We identified 89 drugs requiring compounding for oral administration in children (Fig 1)
- Cardiovascular, central nervous system and anti-infective drugs accounted for 56% of all drugs (Table 3)

- **Regulatory status:**
  - 32 (35%) compounded drugs had a pediatric indication in Canada
    - 11 (34%) were indicated in children <6 years of age
    - 12 (38%) were indicated in children ≥6 years of age
    - 9 (28%) had no specified age in the monograph
  - 57 (64%) compounded drugs were used in children with no Canadian pediatric indication
    - Among those, 26 (46%) had a pediatric indication in the US or the EU

- **Availability of commercial pediatric oral formulations (Table 2):**

Table 2. Commercially available pediatric oral formulations in the US or the EU

Availability of pediatric oral drug formulation	N=89, n(%)
Adequate formulation	20 (22.5)
Suboptimal formulation	20 (22.5)
No suitable formulation	49 (55.0)

Results continued

Figure 1. Regulatory status of oral compounded drugs and commercial availability of pediatric oral formulations

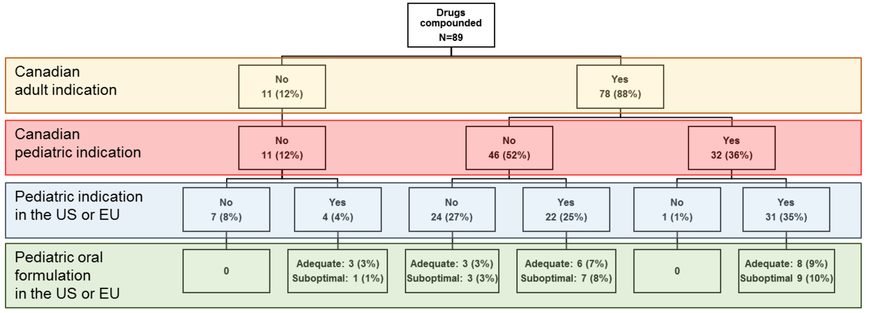

Table 3. American Hospital Formulary Service Pharmacologic – Therapeutic Classification of compounded drugs

AHFS category	N=89 N (%)
Cardiovascular drugs	24 (27)
Central nervous system drugs	16 (18)
Anti-infective agents	10 (11)
Hormones	6 (7)
Autonomic drugs	6 (7)
Vitamins	5 (6)
Gastrointestinal drugs	4 (5)
Electrolytic, caloric and water balance	4 (5)
Immunosuppressive agents	3 (3)
Blood formation and coagulation	3 (3)
Antineoplastic agents	2 (2)
Others	6 (6)

Conclusions

- Significant variability was observed on regulatory status and commercial availability of pediatric oral formulation for drugs requiring compounding in a tertiary pediatric hospital
- Underlying reasons for this heterogeneity need to be better understood
- There is an urgent need for joint guidelines from regulatory agencies to encourage the development of pediatric formulations and facilitate their access to the largest number of children across borders

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