Patient Access to Compounded Drugs in Pediatrics After Discharge from a Tertiary Center

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Background

- Many commonly used drugs are not commercially available in formulations suitable for children.
- Pharmacies have to create new compounds by altering existing adult formulations.
- Timely safe delivery of compounded drugs is challenging.
- Very little is known about the problems faced by patients and their parents with prescriptions of new compounded drugs.

Objective

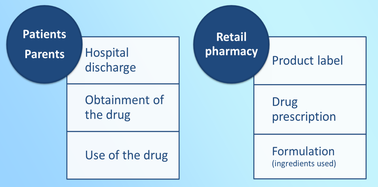
- To describe the problems faced by young patients and their parents when obtaining and using compounded drugs.

Methods

- **Prospective observational descriptive study**
- **Patients**
  - 0 - 21 years of age
  - Discharged from a mother-child tertiary hospital
  - Prescription with ≥ 1 compounded drug
  - Between February 2016 and July 2016
- **Study design and setting**

1. Discharge
2. Telephone follow-up questionnaire 7-10 business days after discharge
3. Contacting the retail pharmacist for additional information
4. Comparison of the dispensed compounded drug with the prescription and published master formulas

- **Data collection**



Definitions

- **Issue:** any inconvenience or concern reported by parents or the research team
- **Discrepancy:** any difference between
  - ⇒ the compounded drug and
  - ⇒ the prescription and/or
  - ⇒ available published compounding master formulas

  A discrepancy was considered as an issue if it could affect the participant
- **Consequences of issues:**
  - ⇒ **None:** issues that were not associated with any risks or if their repercussions could not be established due to the study methodology
  - ⇒ **Minor:** problems associated with risks not leading to any major safety concern
  - ⇒ **Major:** problems associated with risks leading to a major safety concern
- **Problem**:
  - ⇒ Minor or major real or potential consequences

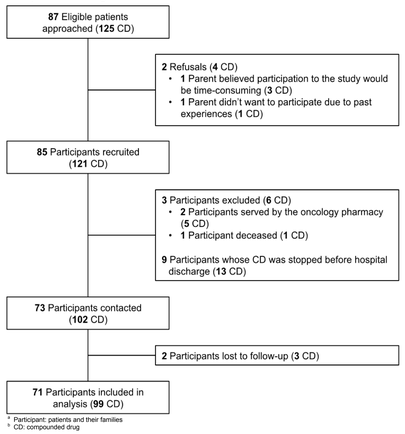
Table 1. Definitions and Examples of Issues by Category

Step	Definition	Examples of issues	Examples of potential consequences
1. Reception of the prescription by the dispensing pharmacy[a]	Searching for a local retail pharmacy able to dispense the compounded dug and handing-out the prescription	• Multiple pharmacies visited, opening hours • Pharmacy's willingness to prepare it (unavailable infrastructure for compounding, missing ingredients, etc.) • Parent delay in handing out the prescription • Pharmacy suggested by a healthcare professional	• Time-consuming process • Delay in drug dispensing
2. Data entry and label creation	Transcription of the prescription information to the pharmacy software (to ensure adequate drug dosing and standard labelling)	• Software not designed for data entry of compounded drugs • Calculation errors • Transcription errors • Treatment duration	• Delay in drug dispensation[b] • Wrong dose or drug regimen • Unclear label • Multiple visits to the pharmacy
3. Prescription validation	Data entry and label verification including: master formula, indication, dosing, interactions, precautions and contraindications	• Selection of the compounding master formula • Scarce data for compounded drug • Delay due to communications with other healthcare professionals	• Delay in drug dispensation[b] • Data entry error not detected[c] • Unknown stability
4. Compounding and packaging	Preparation of the compounded drug according to the available published master formula and packaging including label placement	• Delay or issue related to preparation • Texture of the compounded drug • Wrong packaging (e.g., plastic instead of glass bottle) • Label placement	• Delay in drug dispensing[b] • Ingredients measurement issues[c] • Unknown stability • Wrong label (including auxiliary labels)
5. Dispensing	Serving the compounded drug to the parent with instructions on use by the pharmacists and payment	• Insurance or cost • Tool dispensing • Instruction on use of the drug and measuring tool • Miscommunication between parent and pharmacy staff • Delivery to the patient's residence	• Delay in drug dispensing[b] • Misunderstanding leading to administration issues
6. Use	Usage of the compounded drug by parents		
6.1. Container	Container of the compounded drug (e.g., bottle)	• Cap issues • Size issues	• Inconveniences
6.2. Measuring	Measuring the dose with a tool (e.g., syringe)	• Erasure of the scales on the measuring tool • Inconvenient syringe for administration • Wrong tool used by the parent • Multiple manipulations (e.g., spilling, air bubbles)	• Imprecise dose • Part of dose lost • Time-consuming process
6.3. Administration	Giving the compounded drug to the child	• Unpalatable drug • Improper shaking of suspension • Missed dose	• Compliance, vomiting of the compounded drug • Unreliable dose if suspension not well shaken • Clinical consequence
6.4. Storage	Recommended storage (place and temperature) until BUD[d]	• Improper storage • Misunderstanding of the BUD[d]	• Unreliable or unknown stability[c] • Leading to use of the drug beyond the BUD[d]
7. Other		• Hospital pharmacy issues	• Missed dose

[a] Dispensing pharmacy: dispenses the compounded drug, whether it compounds it or not
[b] May lead to missed dose
[c] May lead to wrong dose or drug regimen
[d] BUD beyond-use date: date beyond which a compounded preparation should not to be used, determined from the date the preparation is compounded (as opposed to the manufacturer's expiration date).

Results

Figure 1. Flow Chart and Follow-Up of Participants[a] and Their Compounded Drugs[b]



[a] Participant: patients and their families
[b] CD: compounded drug

Table 2. Participant[a] and Compounded Drug Characteristics

Characteristic	N
Participant[a] characteristics	**N = 73**
Age at discharge from hospital	
Median (IQR), months	6.9 (13.3)
Maximum, years	11
Number of CDs[b] recruited by participant	
Median (IQR), n	1.0 (1.0)
Maximum, n	4
Male sex, N (%)	46 (63.0)
Discharged from hospital during working days, N (%)	61 (83.6)
Ethnicity, N (%)	
White	49 (67.1)
Arabic	10 (13.7)
Black	5 (6.8)
Aboriginal peoples	2 (2.7)
Other	7 (9.6)
Insurance, N (%)	
Private	50 (68.5)
Public	23 (31.5)
Parental highest level of education, N (%)	
High school	45 (61.6)
College/University	24 (32.9)
Not reported/declared	4 (5.5)
Annual household income, N (%)	
$10,000 - $49,999	20 (27.4)
$50,000 - $99,999	30 (41.1)
More than $100,000	12 (16.4)
Not reported/declared	11 (15.1)
CD[b] characteristics	**N = 99**
Place where CD[b] was prepared, N	
Dispensing pharmacy	62 (62.6)
Compounding pharmacy	18 (18.2)
Unknown	19 (19.2)
CD[b] dispensation, N	
Parent returned to the pharmacy to obtain it	88 (88.9)
CD[b] delivered to the participant's home	8 (8.1)
Parent waited at the pharmacy to obtain it	3 (3.0)

[a] Participant: patients and their families; [b] CD: compounded drug; [c] Includes elementary school, high school, diploma of vocational studies and CEGEP education; [d] Dispensing pharmacy: dispenses the compounded drug, whether it compounds it or not

Table 3. Name, Concentration and Frequency of Compounded Drugs Included in Analysis by OPQ[a] Category

Name and concentration of CD[b] by OPQ[a]	N = 99 (%)
Simple preparations (OPQ[a] Category 1[c])	**75 (75.8)**
Cardiovascular drugs	**34 (45.3)**
Amlodipine 1 mg/ml	11
Sildenafil 2.5 mg/ml	7
Sotalol 5 mg/ml	4
Propranolol 5 mg/ml	3
Others	9
Central nervous system drugs	**17 (22.7)**
Levetiracetam 50 mg/ml	10
Others	7
Gastrointestinal drugs	**8 (10.7)**
Ursodeoxycholic acid 20 mg/ml	5
Domperidone 1 mg/ml	3
Hormones	**7 (9.3)**
Prednisone 5 mg/ml	6
Hydrocortisone 1 mg/ml	1
Others	**9 (12.0)**
Complex preparations (OPQ[a] Category 2[d])	**5 (5.1)**
Vitamins	**5 (100)**
Phytonadione (Vitamin K) 1 mg/ml	4
Calcitriol 0,5 mcg/ml	1
NIOSH preparations (OPQ[a] Category 3[e])	**19 (19.2)**
Immunosuppressive agents	**9 (47.4)**
Tacrolimus 0.5 mg/ml	8
Folinic acid 10 mg/ml	1
Central nervous system drugs	**6 (31.6)**
Topiramate 6 mg/ml	5
Clonazepam 0,1 mg/ml	1
Cardiovascular drugs	**4 (21.1)**
Spironolactone 5 mg/ml	4

[a] *OPQ = Ordre des pharmaciens du Québec* (Quebec Order of Pharmacists)
[b] CD = compounded drug
[c] Simple preparations made without hazardous drugs or substances
[d] More complex preparations requiring particular techniques
[e] Preparations made with hazardous drugs or substances as classified by the National Institute for Occupational Safety and Health (NIOSH)

Table 4. Barriers to Obtaining the Compounded Drug

End Point	
Number of families who visited multiple pharmacies	8
Number of visited pharmacies	
Median (IQR), N	1.0 (0.0)
Maximum, N	4
Reasons for changing pharmacy, N = 16 (%)	
Referral to another pharmacy due to:	9 (56.3)
• Unavailable or inappropriate equipment	8
• Could not prepare this CD[a]	1
Delay in drug dispensation due to:	4 (25.0)
• Need to order the CD[a]	1
• Need to order missing products	1
• Pharmacy closed for holidays	2
Refusal to prepare the CD[a]	3 (18.8)
Duration from ordering to obtaining the CD[a]	
Median (IQR), hours	24.0 (66.0)
Minimum, hour	0.5
Maximum, days	12
Reasons for the delay, n = 95 (%)	
Time-consuming preparation	30 (31.6)
Missing ingredient:	25 (26.3)
• Missing CD[a]	14 (56.0)
• Missing products	11 (44.0)
Parents said they would return to the pharmacy later	4 (4.2)
Busy with other drug preparation	3 (3.2)
Other[b]	7 (7.4)
Unreported reason	26 (27.4)
Number of patients who missed doses	1

[a] CD = compounded drug; [b] Reduced staff, missing or busy with another task; pharmacy closed during holidays; insurance coverage; pharmacy forgot to call when compounded drug ready; staff wanted to discuss with pharmacy owner the next day.

Table 5. Issues Reported by Parents Per Compounded Drug and Severity of Consequences

Issue	No. (%)	Consequences (N = 147)		
		None	Minor	Major
1. Reception of the prescription by the dispensing pharmacy[a]	10 (6.8)	1	9	
2. Data entry and label creation	18 (12.2)	2	16	
3. Prescription validation	1 (0.7)		1	
4. Compounding and packaging	18 (12.2)		16	2
5. Dispensing	29 (19.7)	3	25	1
6. Drug use	63 (42.9)	28	32	3
6.1. Container	5 (7.9)	5		
6.2. Measuring	38 (60.3)	15	21	2
6.3. Administration to the child	17 (27.0)	8	8	1
6.4 Storage	3 (4.8)		3	
7. Other	8 (5.4)		8	
Total	**147**	**34**	**107**	**6**
Total of problems			**113**	

[a] Dispensing pharmacy: dispenses the compounded drug, whether it compounds it or not

Table 6. Discrepancies and Associated Issues Identified by the Research Team and Severity of Consequences and Associated Problems

Variable	Discrepancies, No. (% of total)	Issues, No. (% of discrepancies)	Consequences (N = 75)		
			None	Minor	Major
Name/formulation and concentration (N = 98)	15 (7.9)	4 (26.7)		3	1
Ingredients and quantities (N = 87)	31 (16.4)	16 (51.6)		15	1
Dose (N = 99)	5 (2.6)	4 (80.0)		2	2
Drug regimen and administration route (N = 99)	17 (9.0)	4 (23.5)	1	3	
Treatment duration and number of refills (N = 99)	36 (19.0)	17 (47.2)		17	
Beyond-use date (N = 98)	26 (13.8)	7 (26.9)		7	
Storage (N = 98)	4 (2.1)	3 (75.0)		3	
Conditioning (N = 98)	3 (1.6)	1 (33.3)		1	
Use informations/ instructions (N = 98)	37 (19.6)	18 (48.6)		18	
Appearance (N = 94)	15 (7.9)	1 (6.7)[a]		1	
Total	**189**	**73[a,b,c]**	**0[c]**	**70[a,b]**	**3[c]**
Total of problems				**73**	

[a] One appearance problem not counted because it was already reported by parent
[b] One drug not dispensed as a compounded drug, considered as a problem because of no data on stability *(see Appendix 1)*
[c] One dose problem caused a drug regimen problem and one ingredient quantity problem caused a dose problem (they have been counted as only one problem each)

Table 7. Issues Reported by the Research Team Per Compounded Drug at the Interview and Severity of Consequences

Issue	No. (%)	Consequences (N = 94)		
		None	Minor	Major
1. Reception of the prescription by the dispensing pharmacy[a]	13 (13.8)	5	8	
2. Data entry and label creation	2 (2.1)		2	
3. Prescription validation	2 (2.1)		2	
4. Compounding and packaging	5 (5.3)		5	
5. Dispensation	51 (54.3)	21	30	
6. Drug use	8 (8.5)	1	7	
6.1. Container	0 (0.0)			
6.2. Measuring	3 (37.5)	1	2	
6.3. Administration to the child	1 (12.5)		1	
6.4. Storage	4 (50.0)		4	
7. Other	13 (13.8)	1	12	
Total	**94**	**28**	**66**	**0**
Total of problems			**66**	

[a] Dispensing pharmacy: dispenses the compounded drug, whether it compounds it or not

Recommendations

1) Standard measures at discharge should be implemented, such as delivering an adequate quantity of drug, contacting retail pharmacists to ensure continuity of care by the hospital pharmacists, and sensitizing prescribers to the importance of pharmacists to prepare the hospital discharge.

2) Softwares adapted for drug compounding should be implemented and guidelines should be developed to standardize the content of drug labels.

3) Compounding master formulas should be standardized to avoid variability in content.

4) The price of compounded drugs and the reimbursement process should be standardized.

5) Standardized written information about the utilization and storage of the compounded drug, and use of the measuring tools should be provided to families.

6) Incentives can be used to encourage pharmaceutical companies to develop drugs adapted to the pediatric population and reduce the need to compound drugs.

Conclusion

- This study is the first to show that compounding-related problems are frequent and can arise at every step of drug preparation, obtainment and use.
- The risk for patient's safety is significant despite the effort and the individualized care of the hospital pharmacist, suggesting that current practice standards are insufficient and suboptimal to ensure adequate patient safety.
- Health authorities around the world should replicate similar studies, implement measures to improve patients' safety and develop incentives to motivate the development of commercial products adapted to children's unique needs.
- When compounding is required, nationwide standardized master formulas, based on the best published data, should be used in order to reduce risks and confusion.

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