

Off-Label Prescribing: Medication Errors and Formulation Related Limitations

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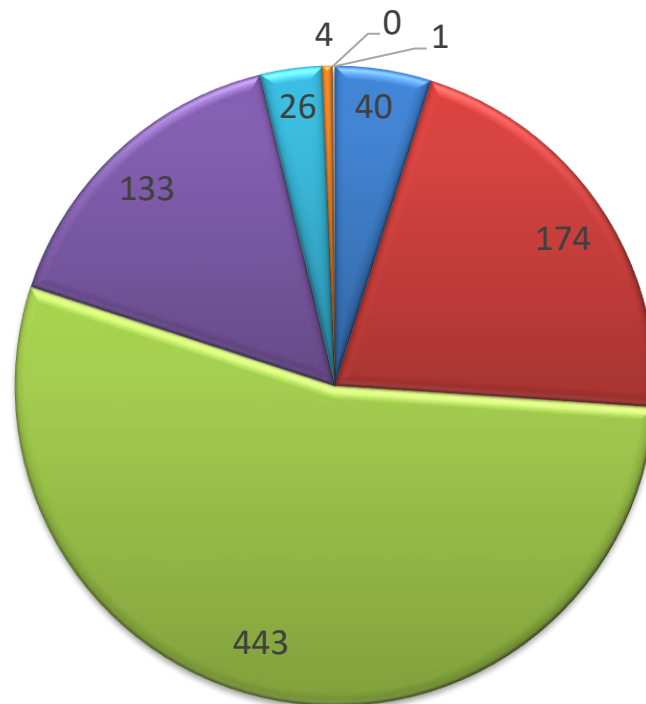
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Objectives

- Describe documented errors and known risks with antihypertensive medications in pediatrics
- List newer dosage forms in the antihypertensive space
- Discuss possible solutions and ongoing efforts to improve dosage forms for children

Cardiovascular Medication Errors in Children

Medication Error Harm Scale



■ A: no error, capacity for error

■ C: error, reached patient, no harm

■ E: error, temporary harm, intervention

■ G: error, permanent harm

■ B: error, did not reach patient

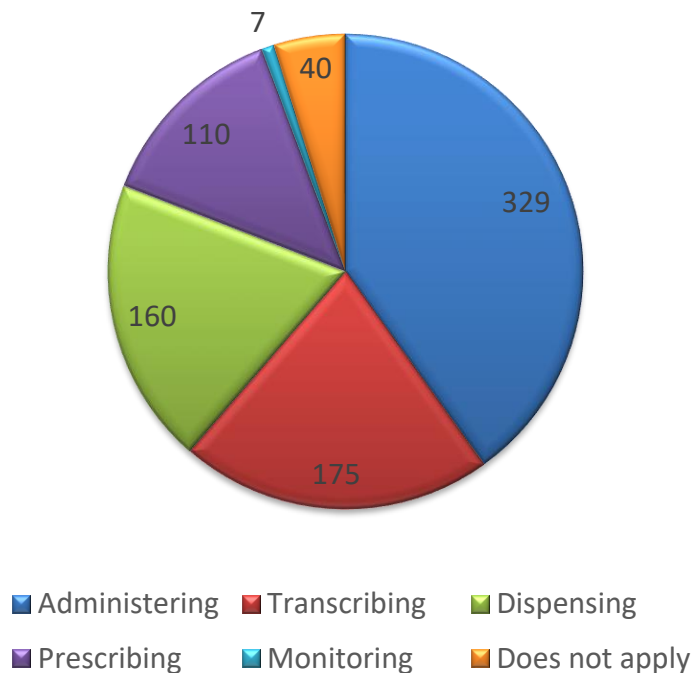
■ D: error, monitoring required, no harm

■ F: error, temporary harm, prolonged hospitalization

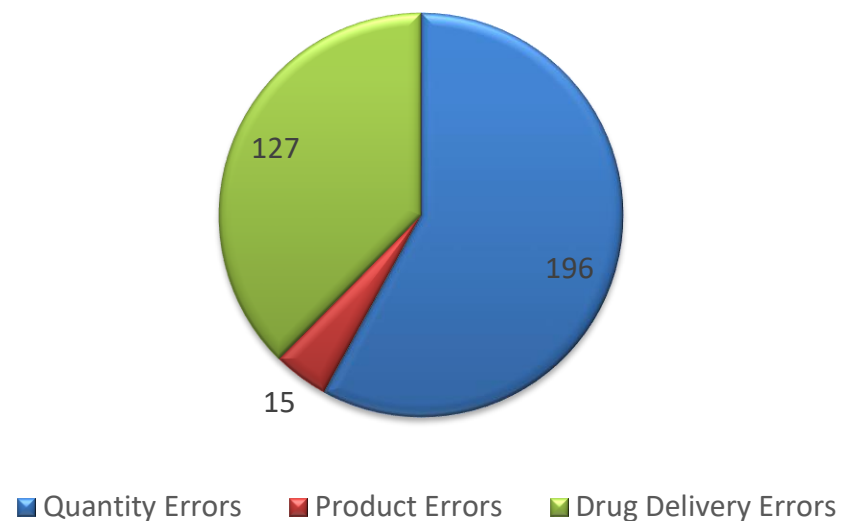
■ H: error, life-sustaining intervention

Cardiovascular Medication Errors in Children

Error Node



Administering Errors

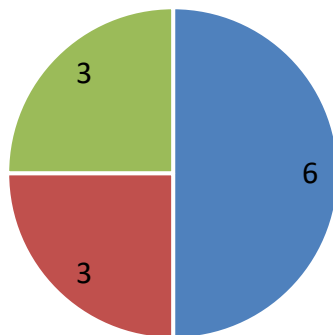


Quantity errors: extra dose, improper dose/quantity, omission error, prescribing error

Antihypertensive Medications for Children: Where are we now?

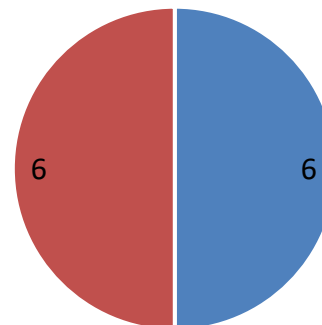
Medication		FDA Approved Age	Dosage Forms Available
Alpha-adrenergic agonist	Clonidine	Adults (XR suspension and XR tablets for ADHD approved in 6 years +)	Oral solution, tablets (XR suspension and XR tablets for ADHD)
ACE-Inhibitors	Captopril	Adults	Tablets
	Enalapril	Tablets: Adults Oral solution: adults & children older than one month	Oral solution, tablets
	Lisinopril	Tablets & Oral solution: adults & children 6 years and older	Oral solution, tablets
Angiotensin II Receptor Blockers	Candesartan	Tablets: 1 year and older	Tablets
	Losartan	Tablets & Oral solution: adults & children 6 years and older	Oral suspension, tablets
	Valsartan	Tablets: 1 year and older Oral solution: adults & children 6 years and older	Oral solution, tablets
Calcium Channel Blockers	Amlodipine	Tablets, oral solution & suspension: adults & children 6 years and older	Oral solution, oral suspension, tablets
	Isradipine	Adults	Capsules
	Nifedipine	Adults	XL tablets, IR capsules
Vasodilators	Hydralazine	Adults (pediatric dosing given)	Tablets
	Minoxidil	Adults (pediatric dosing given as a “rough guide”)	Tablets

Number of Antihypertensive Medications by Age Group



- Adults Only
- Adults & Children 6 years and up
- Adults and Children 1 month or 1 year and up

Dosage Forms Available for Antihypertensive Medications



- Solid dosage forms only
- Solid & liquid dosage forms

What do we do when we don't have a liquid?

- Use tablets – round to the nearest $\frac{1}{2}$ tablet
 - Crush and mix in liquid/food
 - Do families have access to an appropriate pill splitter / crusher?
 - How can we administer to an infant who is fed by bottle?
 - Crush and mix in water? Breast milk/formula?
- Compound a liquid
 - Access to a compounding pharmacy?
 - Insurance coverage?

Clonidine Compoundir



Report a med error

Case Reports

> [Pediatrics](#). 2001 Aug;108(2):471-2. doi: 10.1542/peds.108.2.471.

> [Education](#) [Resources](#)

A 1000-fold overdose of clonidine caused by a compounding error in a 5-year-old child with attention-deficit/hyperactivity disorder

M J Romano ¹, A Dinh

Massive clonidine overdose
due to a pharmacy compounding error
on investigating suspected

Continue to Harm Children

Compounding is a high-risk process, and the associated complexity can increase the likelihood of medication errors. This bulletin describes two recently reported medication incidents that involved the preparation of clonidine suspension by different methods.

Brian Patrick Murray ¹, Matthew David Sheridan ², Hannah Hays ³



5-year-old Kentucky girl remains in ICU after taking potentially bad batch of clonidine

BMJ Case Reports 2025;18(8):e266965.

WLKY. <https://www.wlky.com/article/kentucky-clonidine-child-hospital-wlky-investigates/62021298>

Nifedipine Immediate Release Capsules



Liquid Medicines, still the answer?



Taste/Smell/Volume: Clindamycin

- Commonly used antibiotic for skin infections, pneumonia
- Administration issues
 - Taste – very bitter
 - Smell – unpleasant
 - Concentration – very dilute
 - 75 mg / 5 mL
 - A 12-month-old, 10 kg patient would receive 100mg PO TID, which is 6.7 mL PO TID
 - A 5-year-old, 20 kg patient would receive 200 mg PO TID, which is 13.3 mL PO TID
- Dose – Frequent dosing, long course
 - TID x 10 days

Still more problems with liquids

- Shelf life – especially after reconstitution
- Oral syringes and the need for adapters
- Osmolarity of oral liquids for premature infants



Image 1. Without adapter



Image 2. With adapter

Multiparticulates

- Solid dosage forms consisting of small discrete units
- Usually 2.5 mm or less
- Terms include pellets, granules, mini-tablets



Can Neonates Take Them Safely?



Figure 5. Newborn child with uncoated mini-tablet in the cheek pouch before swallowing.



Acceptability of Uncoated Mini-Tablets in Neonates—A Randomized Controlled Trial

Viviane Klingmann, MD¹, Annika Seitz, MD candidate¹, Thomas Meissner, MD¹, Jörg Breitzkreutz, PhD²,
Andreas Moeltner, PhD³, and Hans Martin Bosse, MD¹

Open, randomized, prospective cross-over
study to compare the acceptability and
swallowability of 2mm uncoated mini tablets
with 0.5 mL of oral syrup

Ages 2-28 days

N=151

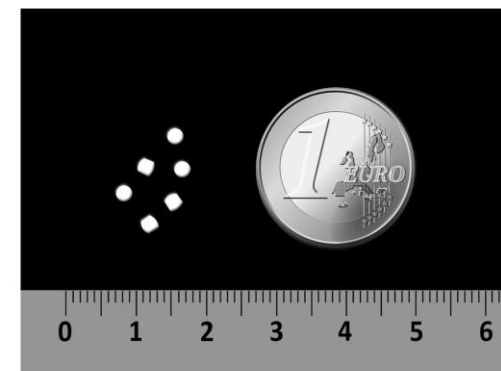


Figure 2. Dimensions of 6 uncoated mini-tablets (left) in relation to a 1 Euro coin (right).

Table. Assessment of the total population and the subgroup of preterm neonates

Evaluation criteria	Mini-tablets, N (%)	Syrup, N (%)	Noninferiority test	Two sided test
Total population				
Everything swallowed	124 (82.1)	109 (72.2)	$P < .0001$	$P = .0315$
Partially swallowed	27 (17.9)	42 (27.8)		
Choked on	0 (0)	0 (0)		
Termination	0 (0)	0 (0)		
Total	151 (100)	151 (100)		
Subgroup: preterm neonates				
Everything swallowed	9 (81.8)	8 (72.7)	ND	ND
Partially swallowed	2 (18.2)	3 (27.3)		
Choked on	0 (0)	0 (0)		
Termination	0 (0)	0 (0)		
Total	11 (100)	11 (100)		

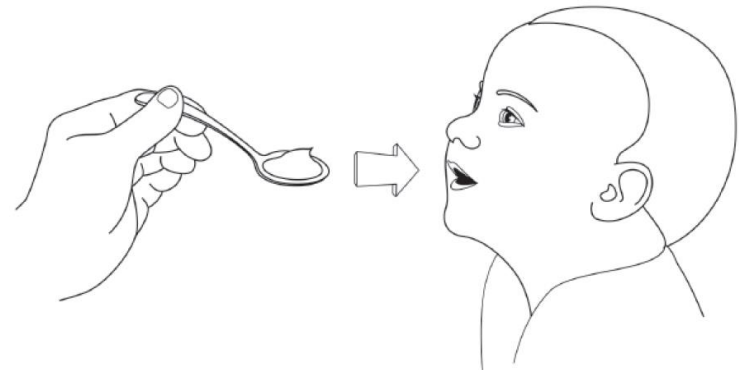
ND, not determined.

In total, 151 neonates were investigated. Swallowability (criterion 1) was significantly higher for mini-tablets compared with syrup. The proportion of the 11 preterm neonates swallowing the mini-tablet completely is similar to the total population.

Current Multiparticulate Use in Pediatric Cardiovascular Medicine

Pradaxa® (dabigatran etexilate) oral pellets

- Available as oral pellets: 20mg, 30mg, 40mg, 50mg, 110mg, 150mg per packet
- Approved for
 - Treatment and prevention of recurrence of VTE ages 3 months - <12 years



Rivaroxaban

Find your dose line.

You can use either side of the syringe to set your dose.

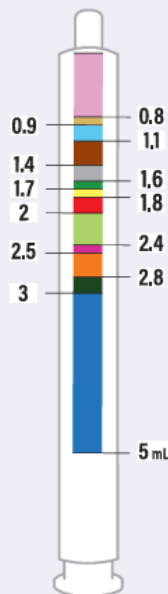
If using mL side of syringe:

Top of the plunger should line up with the prescribed mL.

If using color side of syringe:

Top of the plunger should line up with the prescribed mL dose line at the **bottom of the color band**.

Only use the oral dosing syringe provided with XARELTO oral suspension.

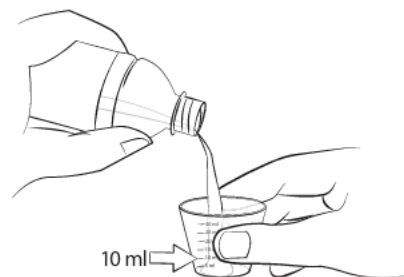


If your dose is more than 5 mL.

You will need to use the same syringe more than one time. Repeat Steps 4 and 5 to complete your dose. Ask your pharmacist if you are not sure.

Dose	Measure
7.5 mL	5 mL + 2.5 mL
10 mL	5 mL + 5 mL
15 mL	5 mL + 5 mL + 5 mL
20 mL	5 mL + 5 mL + 5 mL + 5 mL

Apixaban



5–7 minutes



Push plunger all the way down.



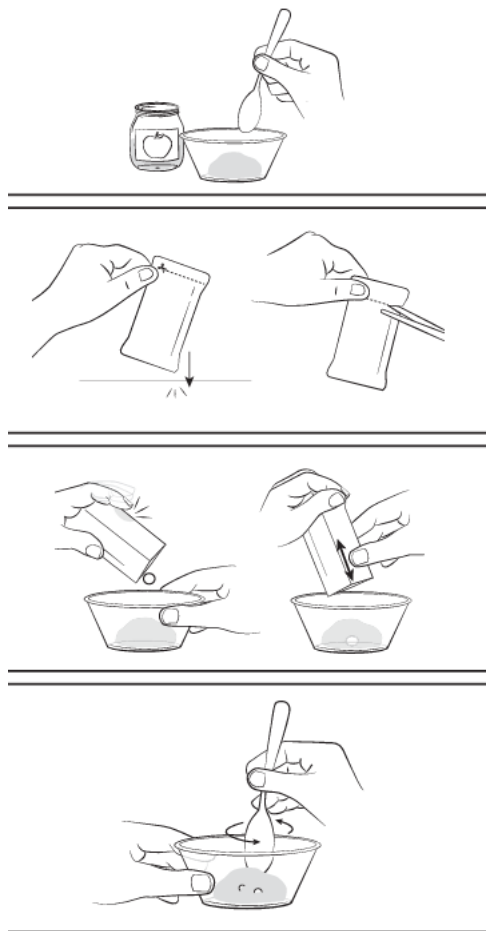
Place the syringe tip into the cup and pull up all the liquid mixture.



With the child seated upright or slightly inclined (tilted back), place the oral syringe into the mouth with the tip along either cheek. Slowly push the plunger all the way down to give all medicine in the syringe.



Apixaban



Summary

- Errors with cardiovascular medications can be particularly dangerous
 - Dosage form manipulation/compounding increase the risk for errors
- Only one medication for hypertension approved for children younger than 6 years old
- Dosage forms are limited to liquids and most are for 6 years +
- Solid oral dosage forms won't solve all problems, rather they will have their own challenges (i.e. tubes)

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