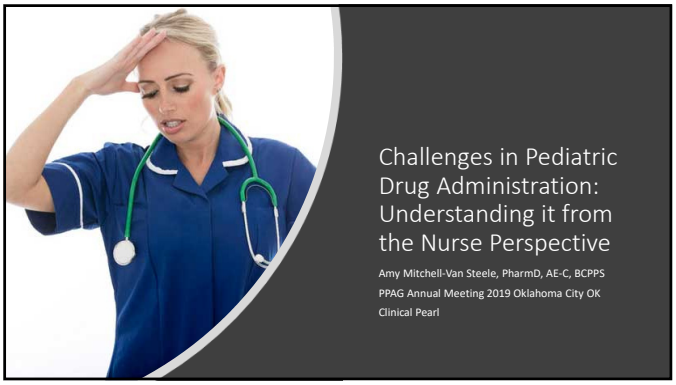

Challenges in Pediatric Drug Administration: Understanding it from the Nurse Perspective

Amy Mitchell-Van Steele, PharmD, AE-C, BCPPS

PPAG Annual Meeting 2019 Oklahoma City OK

Clinical Pearl

1

Objectives

- Understand the challenges relating to drug manipulation when done as a means to achieve smaller pediatric doses
- Discuss the literature relating to drug manipulations
- Describe suggested procedures for administering partial doses
- Describe potential electronic record/order entry implications

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Disclosures

- Speaker has no financial conflicts to disclose
- Speaker also claims not to have any of the "right" answers, only suggestions relating to solutions for the challenges discussed

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Overview of the Challenges

1. Many drugs are not provided in pediatric friendly forms
2. Lack of standard procedure for manipulating drugs to provide smaller doses
3. Approach to giving partial doses is different between nurses
4. The HOW may not be a simple process
5. Unintended consequences such as altered pharmacokinetics, altered taste, medication errors, wrong dose, exacerbated side effects

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Manipulation of drugs: *How often is it done?*

- Observational study[1] of drug manipulations followed by a questionnaire of pediatric nurses
  - Aim of study was to scope which drugs and dosage forms are routinely manipulated in practice
  - Also investigated motivation for the manipulation and concerns by those involved
- Total of 498 manipulations were identified
  - Most common dose forms included **tablets** (61.6%, 45.7%), intravenous injections (21%, 11.7%), **sachets** (9.7%, 1.1%), **transdermal patch** (3.2%, 10.6%), and **suppository** (1.9%, 8%)
  - Most common reasons reported for manipulation included no suitable preparation or strength available (55%), patient preference (6.9%) and usual practice (12.2%)
  - Manipulations most commonly occurred in the neonatal, PICU and surgical units
- **Drug manipulation is time consuming, inaccurate and may negatively impact the stability and bioavailability of the drug**

[1]BMC Pediatrics 2013; 13: 81-89

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Manipulation of drugs: *Is there any support in the literature?*

- Authors conducted systematic review of the literature to establish the evidence base for drug manipulation to obtain the required dose
- Studies were potentially eligible if they involved any drug being manipulated by any means
- Excluded if ultimately the entire dose form was administered in a single dose (unless this lead to altered bioavailability or safety of the modified-release tablet) or if the study was related to extemporaneous compounding
- Primary outcome: Dose accuracy as measured by drug content assay or other means such as weight
- Secondary outcomes: evidence of safety or harm due to the manipulation, bioavailability, stability of drug, patient experience with the manipulation, drug exposure due to manipulation or comparison of manipulation methods
- 50 studies were included: 49 involved splitting of tablets and 1 involved suppositories
- **Limited evidence to support widespread clinical practice of drug manipulation**

[2]Int J Pharm 2017; 518: 155-166

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World Health Organization's Advice

- **Children should have access to authorized, ready-to-use, age-appropriate preparations of medicines**
- Compounding of medications should be a last resort; thereby, reducing it's associated risks
- Consider alternatives to compounding which may be safer
  - "Dose rounding"
  - Consider therapeutic alternatives
  - Tablet splitting
  - Tablet/capsule dispersion
  - Crushing tablets/opening capsules and mixing powder with food or drink
  - Use injectable form by the oral route
  - Splitting suppositories
  - Consider alternate routes

https://www.who.int/medicines/areas/quality_safety/quality_assurance/ProvisionHealthCareProfessionals_QAS11-399Rev1_17082011.pdf

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Challenge #1: Splitting tablets

Manipulation of a tablet for dose accuracy was defined by Richey et al as split/broken/cut and a segment given OR crushed and a proportion of the powder given OR dispersed in liquid and a portion of the liquid given

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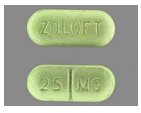
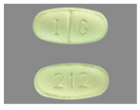
Splitting Tablets: FDA Words of Advice

- Tablet is FDA-approved for splitting:
  1. information printed in "HOW SUPPLIED" section of the professional label insert and the patient package insert
  2. tablet has a score line
- Only since 2011 has the FDA begun to address the equality of both halves of a given tablet
- Switching from one brand to another only guarantees equal content of the <u>whole</u> tablet – not split-ability

Drug : **SERTRALINE**
Strength : **25 MG = 1 TAB**
Dose : **12.5 MG = 0.5 TAB**
Route : **ORAL**
Sig : **1XDAY**





https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/ucm184666.htm

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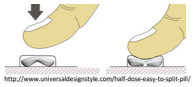
What we know

Assumptions

- ½ tablet = ½ dose, etc.
- If the tablet has a score line, you can split it
- With a pill splitter, anyone can cut a tablet



http://www.universaldesignstyle.com/half-dose-easy-to-split-pill/

Wouldn't it be nice with a push of your finger……

Reality

- Unless specifically tested by the FDA, this may not be true; research shows 30%-100% of halved tablets meet this requirement (Int J Pharm 2017; 518: 155-166)
- Score lines may enable easier splitting but FDA testing for split tablets is only recommended not mandated
- ISMP and FDA recommend tablet splitting be restricted to healthcare professionals
- Even with a proper pill splitter, pills may fracture and break unevenly

https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/ucm184666.htm
P&T 2010; 35(2): 69-70
Guidance for Industry – Tablet Scoring: Nomenclature, Labeling and Data for Evaluation FDA/CDER 2013
JPPT 1999; 4(1): 38-42

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[Giving a portion of the pill] Suggested Procedure

1. Confirm this tablet should be split!
2. Using gloves, place the tablet into the pill splitter
3. Align the grove or "score" with the razor blade
4. If quartering tablet, center tablet portion beneath blade
5. Clean pill splitter with alcohol wipe when done (restrict to single patient use)

- *Only cut what you need as you go, since partial tablets may be less tolerant of storage conditions*

Always use a pill splitter, never scissors or a kitchen knife

http://www.safemedication.com/safemed/PharmacistsJournal/TheDosandDontsofTabletSplitting.aspx

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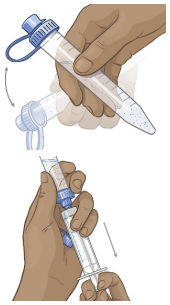
[Dissolving the pill and giving a portion of the solution] Suggested Procedure

1. Place the tablet(s) into dissolve and dose container.
2. Add water up to the container.
3. Replace the blue cap.
4. Allow the tablet to dissolve over a five-minute period, shaking the container a few times during this period.
5. Shake until the pieces of the tablet are gone (some fine powder may remain)
6. Using the oral syringe provided, draw dose into an oral syringe
7. Discard any liquid left in the container.

- *Each dose of medication must be freshly prepared each time and cannot be saved. Wash the Dissolve and Dose in warm soapy water and allow it to air dry*



Also useful for opening and dissolving capsule contents

https://www.aboutkidshealth.ca/Article - use of dissolve and dose containers

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"Dispersible tablets can yield inconsistent doses when withdrawn from different depths of the container."

Example. Prevacid Solutab® – not suitable as a shortcut means for making a solution

BMC Pediatrics 2013; 13: 81-89

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Trouble with the electronic medical record

Challenge

- Manual dose rounding
- Procedure for dose manipulation must be added to clinical directions unless published elsewhere
- Lack of a prompt for tablets that should not be crushed, split or dissolved
- No guidance for specific procedure (tablet splitter versus dissolve-a-dose)

Possible solution

- Design CPOE to use pre-determined portions of tablets
- Directions for dose manipulation can be built into CPOE
- More robust drug information and clear clinical directions will warn the nurse of this bad practice
- Drug information resources can be expanded to include this on a case-by-case basis; specific procedures can also be published in hospital formulary

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Challenge #2: Partial Powder Packets (sachets)

Manipulation of a sachet for dose accuracy was defined by Richey et al open, dispersed in liquid and a portion of the liquid given OR opened and a portion of the powder given

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What we know

Currently, there is no literature describing HOW this should be done and no recommendations from the FDA

Assumptions

- If the resulting solution is clear, the drug fully dissolved and the portion of liquid is proportional to the dose desired
- Estimation of a powder is accurate using a measuring cup in leu of a scale

Reality

- This is only true if the powder is water soluble or if the suspended drug is measured before it falls out of solution
- Directions involve mixing in water but no reference to taking a "partial" dose
- Use of medication-specific measuring cup is acceptable but the universal medication cup has not been validated for powders (tapered in design)

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Medications available as unit-dose powders or sachets commonly used in children			
Generic	**Brand**	**Unit Dosage**	**Water soluble?**
Electrolytes/vitamins			
Sodium phosphate - potassium phosphate	Neutra-Phos	250mg phosphate	Yes
Anticonvulsants			
Vigabatrin	Sabril	500mg	Yes
Hypercholestrolemia medications			
Cholestyramine	Questran	4g	No
Gastrointestinal Agents			
Omeprazole	Prilosec	2.5mg or 10mg	No
Pantoprazole	Protonix	40mg	No
Polyethylene Glycol	Miralax	17g	No

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Medications available as unit-dose powders or sachets			
Generic	**Brand**	**Unit Dosage**	**Water soluble?**
Analgesics/Cough and Cold			
Acetaminophen-aspirin - caffeine	Goody's Headache powders	260mg – 520mg – 32.5mg	Aspirin = no
Aspirin - caffeine	BC Original	845mg – 65mg	Aspirin = no
Diclofenac	Cambia	50mg	Sometimes
Acetaminophen-dextromethorphan - phenylephrine	Theraflu	650mg – 20mg – 10mg	Moderately (better in warm/hot water)
Antimicrobial			
Azithromycin	Zithromax	1g	Sparingly – not recommended for children
Ritonavir	Norvir	100mg	No – intended to be sprinkled on food

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Medications available as unit-dose powders or sachets			
Generic	**Brand**	**Unit Dosage**	**Water soluble?**
Electrolytes/vitamins			
Vitamin C (ascorbic acid)		1000mg	Yes
Calcium citrate		600mg	Sparingly
Sodium phosphate - potassium phosphate	Neutra-Phos	250mg phosphate	Yes
Patiromer	Veltassa	8.4g	No – recommended to sprinkle on food
Anticonvulsants			
Vigabatrin	Sabril	500mg	Yes

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Medications available as unit-dose powders or sachets			
Generic	**Brand**	**Unit Dosage**	**Water soluble?**
Hypercholestrolemia medications			
Cholestyramine	Questran	4g	No
Colesevelam	Welchol	1.875g	Yes
Gastrointestinal Agents			
Dietary Fiber supplements	Metamucil, Benefiber	5.8g/tsp	No
Omeprazole	Prilosec	2.5mg or 10mg	No
Pantoprazole	Protonix	40mg	No
Polyethylene Glycol	Miralax	17g	No

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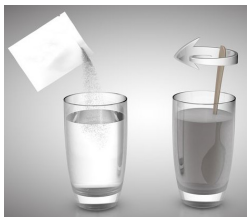
[Dispersion in liquid and give portion] Suggested procedure

1. Confirm powder is water soluble
2. Open packet and dissolve into a pre-determined amount of water (this will make a standard concentration)
3. Shake vigorously
4. Measure the aliquot needed for this patient's dose
5. Discard remainder



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[Measurement of a portion of the powder] Suggested procedure

1. Confirm availability of an accurate measuring device
2. Open packet and pour into a container for weighing or reach into packet with measuring spoon
3. Place portion of powder into liquid of choice to mix for taste
4. Discard remainder

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Trouble with the electronic medical record

Challenge

- Predetermined "recipe" must be added to clinical directions
- Order entry not able to describe drug as a suspension/slurry when dispensed as a powder – portion of powder packet confusing!
- Dose volume is not calculated, at most is manually placed in clinical directions

Possible solution

- Directions for "recipe" can be built into CPOE: dissolve packet in XmL to make suspension of [strength]
- Consider units as just mg or mEq and eliminate reference to packets
- Use of standard doses will allow for this dose volume to be built in

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Trouble with the electronic medical record

Challenge

- Without dose volume, more complicated to round dose
- When using a measuring spoon-like device, must have conversion of grams or milligrams into teaspoons

Possible solution

- Create a "rule" for rounding
- If drug is water-soluble, use procedure for making solution and then giving aliquot; only if drug is water-insoluble, should the powder be weighed and the "conversion" by determined and published in drug information reference

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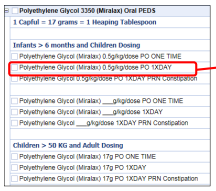
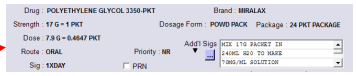
Example Case

- A patient is prescribed polyethylene glycol





Problem 1: Calculated dose yields a partial packet that is not rounded
Problem 2: Polyethylene glycol is not water soluble so mixing solution (as directions imply) and then drawing up a partial dose will yield an unknown amount of drug

Is it too much to just give the patient one packet of 17g?

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Example Case continued

- Let's look to the dosing recommendations: (per LexiComp)

Constipation: Limited data available: Infants, Children, and Adolescents: Oral: 0.2 to 0.8 g/kg/day (NASPGHAN [Tabbers] 2014); higher initial dose of 1 g/kg have been suggested (Loening-Buck 2004; Pashankar 2001); maximum daily dose: 17 g/day. **Note:** Dosage should be individualized to achieved desired effect, infants and young children may require higher doses than school aged children (Loening-Buck 2004; Pashankar 2001)

- While this is consistent with the current CPOE build, it yields partial packets
- Two choices remain:
  1. Determine how to measure portions of the powder easily and consistently on the floor (set up "rounding rules" to this)
     - Does this require special measuring tool? Most floors don't have measuring spoons
     - Would it ever be feasible to measure a half packet and repackage in the pharmacy?
     - Some recommend ⅓ or ¼ portions of the cap but packets are dispensed not the bottle/cap
  2. Determine standard dose using whole packets
     - Still leaves challenge of smaller patients under 17-20kg
     - Possible when higher doses are required as with bowel clean-outs

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Challenge #3: Partial Transdermal Patches

Manipulation of a transdermal patch for dose accuracy was defined by Richey et al as patch cut and portion applied OR portion of patch uncovered and applied

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Transdermal Patches

- **Drug in adhesive layer systems** [a] – drug is homogeneously mixed with a polymer-based adhesive applied to an impermeable backing
  - Cutting the patch will decrease the amount of drug delivered without presenting a hazard
  - Example: Lidocaine
- **Matrix systems** [b] – drug is evenly distributed throughout an adhesive matrix
  - Cutting may be possible but efficacy of adhesive may be compromised
  - Example: Estradiol
- **Reservoir membrane-modulated system** [c] – drug contained in a reservoir between an impermeable backing layer and a rate-controlling microporous membrane
  - Cutting the patch makes the entire dose available immediately
  - Example: Fentanyl
- **Microreservoir systems** [c] – drug is contained in multiple, smaller drug reservoirs
  - Cutting the patch destroys some of he reservoirs, leaving the number of reservoirs disproportionate to the surface of the patch
  - Example: Clonidine

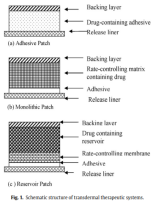

Fig. 1. Schematic structure of transdermal therapeutic systems.

Ball AM, Smith KM. Optimizing Transdermal Drug Therapy AJHP 2008; 65 (15): 1337-1346

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What we know

- The amount of available drug is directly proportional to the surface area of the patch: ½ patch = ½ dose
- Cutting the patch is DANGEROUS in most cases
- Provision of a partial transdermal patch may be achieved by occluding (uncovering) the patch and only adhering the desired portion to the patient

J Opioid Manag 2010; 6(4): 290-294
J Am Vet Med Assoc 2004; 224 (5): 700-705

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Procedure for Partial Transdermal Patch Administration

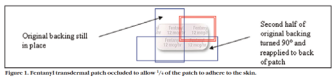

Figure 1. Fentanyl transdermal patch occluded to allow ¼ of the patch to adhere to the skin.

1. Occlude (NEVER CUT) appropriate portion of patch with barrier layer of wax paper or manufacturer's backing (portion of patch exposed to skin should be a measurable fraction such as ⅛, ¼, ½, ⅝, ¾, ¾).
2. Leave barrier edges overlapping (untrimmed) to allow for easier confirmation of portion exposed to skin without having to lift patch.
3. Place on area of skin that has minimal hair (clip, don't shave) where child will have difficulty removing. Take care not to place on the child's back if the child is not likely to change positions and will spend significant time lying against the patch, allowing it too become to warm with resultant potential increased release of drug
4. Date, time, and write fraction exposed to skin on the patch surface (and initial).
5. Cover with transparent dressing to ensure maximal adhesion for next 72 hours.
6. When removing, un-occlude and fold patch on to itself for disposal. Do NOT attempt to "move" occluded area of patch and reuse. The risk of reapplying the used portion is not worth the economy.

J Opioid Manag 2010; 6(4): 290-294

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Trouble with the electronic medical record

Challenge

- Portion of patch is determined by its shape (1/3 is not achievable if oral or round)
- Dosing is not well understood
- Translation of weight-based dose to portion of patch occurs at prescribing step

Possible solution

- Confirm portion of patch is possible before entry
- Ensure dosing is published in drug information reference and built into CPOE – not easily found in the literature; if extrapolating, account for toxic dose and bioavailability differences in routes

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Trouble with the electronic medical record

Challenge

- Lack of a prompt for nursing to know cutting is unsafe
- Prompts for removal must be manually placed as separate orders

Possible solution

- "Don't cut" is a relevant message to add to clinical directions or perhaps a referral to the procedure for administering a partial patch
- Removal orders may be built as an order entry "set" – only relevant for lidocaine as it is understood in most circumstances to involve an exchange for old patch for a new one in a new location

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Challenge #4: Partial Suppositories

Manipulation of a suppository for dose accuracy was defined by Richey et al as cut/split and a segment given

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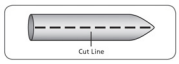
What we know

Currently, there is no literature describing HOW this should be done and no recommendations from the FDA

Assumptions

- It shouldn't matter if cut lengthwise or crosswise



Shape of suppository is designed with a bullet-shaped end for easy entry and the other end flared for retention

Reality

- Dependent upon manufacture process and nature of base, drug may settle and is best divided lengthwise in this circumstance
- Distribution of drug in suppository may be different between manufacturers
- No information or standards
- Bullet shape may be lost in process

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Medications available as suppositories that may be prescribed for children		
Generic	**Brand**	**Unit Dosage**
Acetaminophen	Tylenol, FeverAll	80mg, 120mg, 325mg
Belladonna and Opium		16.2mg – 30mg
Bisacodyl	Dulcolax	10mg
Glycerin		Infant, adult
Prochlorperazine	Compazine	25mg
Promethazine	Phenergan	50mg

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Acetaminophen study

- Anesthesiologists were surveyed about their practice of splitting acetaminophen suppositories
- 10 Anesthesiologists were asked to physically alter 80mg, 120mg and 325mg acetaminophen suppositories into ½ and ⅔ portions
- High-performance liquid chromatography determined drug content
- Study demonstrated that acetaminophen is uniformly distributed in the vegetable oil matrix – cutting lengthwise or crosswise didn't matter
- Alteration of the suppositories resulted in a wide variation in doses
- **Authors concluded that a lack of accuracy and precision in altering suppositories makes a compelling reason to restrict acetaminophen to unaltered suppositories**

Anesth Analg. 2005 May;100(5):1303-5

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More on Acetaminophen

- Acetaminophen suppositories have evenly distributed drug content
- Standard dosing is possible (at least outside the NICU)

Rectal:

Weight-directed dosing: Limited data available: Infants and Children <12 years: 10 to 20 mg/kg/dose every 4 to 6 hours as needed; **do not exceed 5 doses in 24 hours** (Kliegman 2011; Vernon 1979); maximum daily dose: 75 mg/kg/day

Fixed dosing:

Infants 6 to 11 months: 80 mg every 6 hours; maximum daily dose: 320 mg/**day**

Infants and Children 12 to 36 months: 80 mg every 4 to 6 hours; maximum daily dose: 400 mg/**day**

Children >3 to 6 years: 120 mg every 4 to 6 hours; maximum daily dose: 600 mg/**day**

Children >6 up to 12 years: 325 mg every 4 to 6 hours; maximum daily dose: 1,625 mg/**day**

Children ≥12 years and Adolescents: 650 mg every 4 to 6 hours, maximum daily dose: 3,900 mg/**day**

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[Measurement of a portion of the suppository] Suggested procedure

1. May wish to place in refrigerator for a few minutes to minimize melting
2. Remove foil – may help maintain shape during cutting but there is a risk a portion of the foil may be left in the portion of suppository and administered to the patient
3. Use gloves not just for cleanliness but to keep drug off fingers
4. Grasping securely, use a sharp scalpel or equivalent to cut cleanly
5. Discard remainder

Wouldn't it be nice if they came with a score line……

Example of dividable stick-shaped suppositories

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Trouble with the electronic medical record

Challenge

- Not every strength of the suppository is stocked
- Rounding is often not done
- No guidance as to correct procedure for partial dose

Drug :	ACETAMINOPHEN SUPP
Strength :	120 MG = 1 SUPP
Dose :	78 MG = 0.65 SUPP
Route :	RECTAL
Sig :	Q4H PRN
Reason :	FEVER

If only the 80mg suppository had been available for this patient!

Possible solution

- Expand your inventory to include even the 80mg acetaminophen suppository
- If standard dosing is used, only necessary in the NICU and CPOE can be built to include a standard portion of suppository
- Establish a procedure and publish in your drug information reference

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Trouble with the electronic medical record

Challenge

- May not have a appropriate surface or tool for splitting suppositories
- Lack barcodes and often proper labeling

Possible solution

- Work with nursing colleagues to ensure the procedure can be properly executed by stocking their medication rooms/areas with a cutting tool and "cutting board"
- Medications without a commercial barcode pose issues:
  - Use laminated barcode card in medication room
  - Pharmacy-added sticker that provides barcode

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Role of the pharmacist

- Round the dose to a measurable portion
- Share directions for making solution with the nurse
- Enter the drug volume that the nurse measures in the clinical directions
- Create policies and procedures relating to the manipulation of dosage forms
- Look for alternatives to drug manipulation

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Final Reflection

"By inappropriately crushing tablets or opening capsules, healthcare professionals could be legally held to account for any harm caused by this action." https://www.rosemontpharma.com/health-professionals/legal-aspects-of-medicines-manipulation

Drug manipulation is standard of care for achieving partial doses for children, but doing so leads to unlabeled use of the medication

The potential lack of accuracy during these manipulations may mean that the actual dose delivered is unknown.

Avoid drug manipulations whenever possible

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Thank You!

Thoughts?

Please feel free to share your ideas and practices.

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