Pediatric Pearls for Ambulatory Practice
Margaret M. Burke, Pharm.D., BCPPS

Disclosure
• The speaker has no conflicts of interest to disclose.

Objectives
• Summarize the concerns from recent literature about the effects of commonly used over the counter (OTC) antipyretics on children.
• Discuss the role of antihistamines, decongestants, and cough suppressants in children including the proper dosing of commonly available products.
• Explain the proper use of oral rehydration to treat dehydration in children.
• Describe methods to promote safe and accurate measuring of pediatric liquid formulations.
• Recognize issues surrounding medication dosing in obese children.

Antipyretics

Goal of Antipyretic Therapy
• Improve overall comfort and well-being of child
• Maintain activity and feeding
• NOT to maintain normal body temperature
• Fever (rectal temp > 100.4°F) is a beneficial response

Febrile Patients to Refer
• Infants < 3 months with rectal temp > 100.4°F
• Any child with rectal temp > 104°F
• Immunocompromised child with any fever
• Fever lasting more than 24 hours in children < 2 years
• Fever lasting more than 72 hours in older children
Antipyretic Comparison

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pro</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective analgesic,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antipyretic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe in pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Available as suppository</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indicated in all ages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provides anti-inflammatory properties</td>
<td>Effective analgesic, antipyretic</td>
<td></td>
</tr>
<tr>
<td>Wide therapeutic window</td>
<td></td>
<td>Safe in pregnancy</td>
</tr>
<tr>
<td>2 concentrations available</td>
<td></td>
<td>Available as suppository</td>
</tr>
</tbody>
</table>

| **Con**               |               |           |
| Hepatotoxicity        |               |           |
| Narrow therapeutic window |             |           |
| Renal toxicity        |               |           |
| 2 concentrations available |             |           |
| Avoid in pregnancy especially 3rd trimester |               |           |
| Indicated for age 6 months or > |       |           |

AVICA Trial Design*

- Multicenter, prospective, double-blind, parallel-group design
- 300 children age 12 to 59 months with mild persistent asthma on standardized asthma therapy
- Randomized to standard dose PRN use of antipyretic not > Q6H
- Duration: 48 weeks
- Primary outcome: number asthma exacerbations treated with steroids
- Secondary outcomes: % asthma-control days, albuterol use, unscheduled visits

AVICA Trial Results

- 226 subjects completed trial (116 acetaminophen; 110 ibuprofen)
- 200 of these received at least 1 dose of medication
- No difference in baseline attributes
- No difference in drug exposure (median # doses)
  - Acetaminophen: 7 doses (intqtl range 2 - 15)
  - Ibuprofen: 4.5 doses (intqtl range 1 - 17) (P=0.47)
- No difference in primary outcome (mean exacerbations)
  - Acetaminophen 0.81 vs Ibuprofen 0.87 (P=0.67)
- No difference in any of secondary outcomes

Open-label antipyretic during AVICA

<table>
<thead>
<tr>
<th>Total antipyretics doses</th>
<th>Acetaminophen Group</th>
<th>Ibuprofen Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinded doses</td>
<td>1933 (85.3%)</td>
<td>1293 (89.5%)</td>
</tr>
<tr>
<td>Acetaminophen OL</td>
<td>137 (6.1%)</td>
<td>110 (5.6%)</td>
</tr>
<tr>
<td>Ibuprofen OL</td>
<td>191 (8.4%)</td>
<td>93 (4.8%)</td>
</tr>
</tbody>
</table>

AVICA Trial Limitations

- Use of open-label antipyretic
- Specific population examined, ? external validity
- Asthma medication adherence monitored as part of study
- Not placebo controlled

Prenatal Acetaminophen and Behavioral Problems

- Data from ongoing longitudinal birth cohort (ALSPAC)
- N = 7796 women-child pairs
- Women self reported acetaminophen use in previous 3 months at 18 and 32 weeks gestation and postnatally
- Children’s behavioral status assessed at 7 years of age using SDQ screening tool

Stergiakoul et al. JAMA Pediatrics 2016;170:964-970.
ALSPAC Results

- 5% of children with behavioral problems at age 7
- Exposure at 18 weeks gestation associated with risk ratio 1.2 (CI 1.06-1.37) for conduct problems and 1.23 (CI 1.08-1.39) for hyperactivity symptoms
- Exposure at 32 weeks gestation associated with risk ratio 1.29 (CI 1.09–1.52) for emotional problems, 1.42 (CI 1.25-1.62) for conduct problems and 1.31 (CI 1.16-1.49) for hyperactivity symptoms

Limitations

- Self report of acetaminophen use
- No assessment of dose or duration
- Not controlled for other possible medication exposures
- SDQ score not a clinical diagnosis
- Association does not mean causality

Key Points

- Not every fever needs to be treated with antipyretic
- Acetaminophen and ibuprofen are both effective and safe when used in appropriate patients at the correct doses
- Asthma (mild persistent) does not appear to be a contraindication for the use of acetaminophen or ibuprofen in children
- More research is needed regarding effects of prenatal acetaminophen exposure

Cough/Cold Products

Goals of Treatment

- Supportive care
- Prevent spread of illness
- Provide comfort to infant/child
- Maintain adequate nutrition and hydration
Therapies

- Nasal saline with bulb syringe suctioning before feeding and sleep
- Cool mist humidifier
- Vapor rub
- Increase fluid intake – water is best expectorant
- Antipyretic/analgesic if patient with significant discomfort
- Avoid cough/cold products especially in infants and young children. Little evidence of benefit and risk of adverse effects and accidental ingestions if available in home.
- Cough/cold products can be considered in older children for significant discomfort if one found to be helpful. Limit therapy to only existing symptoms.

RPh Role in Cough / Cold Products

- FDA recommends against use in children < 2 years old.
- Manufacturers voluntarily withdrew labeling for patients < 4 years of age in 2008.
- Many caregivers still choose to administer these products.
- Educate regarding lack of documented effectiveness and potential risks.
- If insistent on use or recommended by pediatrician, educate regarding proper dose, measuring techniques, therapeutic overlap between products, drug interactions.

Dosing for Cough/Cold Components

<table>
<thead>
<tr>
<th>Drug</th>
<th>Individual Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>0.5 mg/Kg</td>
<td>2 x per day</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>0.5 mg/yd</td>
<td>Q4H</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>1 mg/kg</td>
<td>Q6H</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>2 to 3 mg</td>
<td>Q4H</td>
</tr>
<tr>
<td>Determinophan</td>
<td>2 mg/yd</td>
<td>Q6H</td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>2 to 4 mg</td>
<td>Q6H</td>
</tr>
<tr>
<td>Atamoxifen</td>
<td>15 mg/kg</td>
<td>Q4H</td>
</tr>
<tr>
<td>Ergotrin</td>
<td>5 to 10 mg/kg</td>
<td>Q4H</td>
</tr>
</tbody>
</table>

Per Pediatric and Neonatal Dosing Handbook 22nd ed

Cough/Cold Key Points

- Nonpharmacologic measures preferred in younger children.
- If medications used make sure dose is appropriate.
- Minimize error and adverse effect risks by:
  - Limiting drug products to current symptoms
  - Making sure caregiver understands label
  - Making sure caregiver can measure dose accurately
  - Educating caregiver about potential overlap in ingredients.

Oral Rehydration Solutions

Gastroenteritis

- Results in vomiting and diarrhea, +/- fever
- Average twice per year
- 30 million children; 200,000 hospitalized; 300 deaths annually in U.S.
- Most often a viral cause and self-limiting (low-grade fever)
- Bacterial cause: high fever, blood & wbc's in stool more common
- Complications due mainly to dehydration
Evaluating Dehydration

<table>
<thead>
<tr>
<th>症状</th>
<th>轻度 (5%)</th>
<th>中度 (5-10%)</th>
<th>重度 (10-15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>体重丢失</td>
<td>5%</td>
<td>5-10%</td>
<td>10-15%</td>
</tr>
<tr>
<td>黏膜</td>
<td>正常</td>
<td>干燥</td>
<td>干燥</td>
</tr>
<tr>
<td>眼泪</td>
<td>存在</td>
<td>减少</td>
<td>无</td>
</tr>
<tr>
<td>皮肤</td>
<td>正常</td>
<td>换气</td>
<td>换气</td>
</tr>
<tr>
<td>四肢</td>
<td>正常</td>
<td>冷</td>
<td>冷</td>
</tr>
<tr>
<td>尿量</td>
<td>正常 (&gt;1 mL/kg/hr)</td>
<td>减少</td>
<td>最小</td>
</tr>
<tr>
<td>前囟 (6个月以下)</td>
<td>平坦 +/- 洞</td>
<td>平坦 +/- 洞</td>
<td>洞</td>
</tr>
</tbody>
</table>

Oral Rehydration Solutions

- 含有糖来增强盐和水的吸收。不要超过3%，以免增加渗透压负荷。
- 有两种液体：
  - 用于补液的（例如WHO，Rehydralate）含75-90 mEq/L的钠
  - 维持的（例如Pedialyte，Infalyte）含40-50 mEq/L的钠
- 有些可用冷冻形式。
- 可以添加无糖口味到溶液。

Treatment

- 支持性治疗，避免抗泻药。
- 重点是保持水分和电解质平衡。
- 普遍认为：避免果汁，苏打，因为它们没有电解质的渗透压负荷。
- 不吃不喝2到4个小时。24小时内重新进食。
- 开始腹泻时给ORS：每顿腹泻10 ml/Kg。
- 可能需要每5到10分钟给5到10 ml，根据耐受程度增加。
- 对于中度脱水：给估计的脱水不足，作为补液的替代。

An Alternative Solution?

- 647名6到60个月的儿童，有4天以下的V/D（至少3次在24小时内）和轻度脱水。
- 随机分组：苹果味ORS或稀释的苹果汁/首选液体。
- 给予2 L的液体在ED使用，每2-5分钟5 ml，以及在感冒或每50 - 100 ml的呕吐。
- 每天电话F/U（盲法）。
- 复合结果：需要医院访问，IV补液，MD访问，或>3%体重丢失。


Results

- 两组间基本无差异。
  - 平均脱水分数在两组中均为零。
- 治疗失败
  - 苹果汁组（16.7%） vs. OMS组（25%）（P < 0.001）
- IV补液
  - 苹果汁组（9%） vs. OMS组（P < 0.001）

作者假设结果是由于儿童对ORS的拒食。建议使用稀释的苹果汁和首选液体是ORS在轻度脱水儿童中的合适替代品。

ORS Key Points

- 什么对儿童最有效。
- 在轻度脱水用ORS/OMS不太重要。
- 第一例的V/D的最佳介入。
- 促进小体积的频繁补充。
- 监测脱水程度是关键。
Scenario

LB is a 22-month-old healthy girl. Her mother comes to the pharmacy at 9 pm asking for a recommendation b/c LB was sent home early from daycare after she vomited this afternoon. She has had diarrhea x 3 and has a fever of 100.8°C (rectal). She has a call into the on-call pediatrician. The child’s lips look dry and she has tears on her cheeks.

Question

You assess the child as being moderately dehydrated. What fluid should be recommended?

A. Flat soda
B. Half strength fruit juice
C. Oral rehydrating solution
D. Anything the child is willing to take

Question

What is the best option to treat LB’s fever?

A. Acetaminophen
B. Ibuprofen
C. No treatment
D. A or B

Measuring Liquids Accurately

Current Recommendations

- Use dosing tool with standard markings (AAP/FDA)
- Use milliliter system only (AAP/ISMP)
- All OTC oral liquids should include a measuring device (FDA)
- OTC label and measuring device units should match with no extra markings (FDA)

Johnson and Meyers 2016

- Evaluated Rx oral liquid meds dispensed over 6 month period in a community setting for inclusion of a measuring device and use instructions
- 49/382 (12.8%) included a measuring device
  - Calibrated dropper most common, oral syringe second
- 20/49 (40.8%) included use instructions
- 70/333 (21%) without device included instructions to RPh
Yin et. al. 2016 Design

• Examined how dosing error rates were affected by dosing tool and prescription label units of measure
• English and Spanish speaking parents at 3 large urban clinics across US randomized to 1 of 5 arms by pairings of units of measure on label and device (n = 2110). Health literacy assessed.
• Parent observed measuring 9 doses
  • Volumes: 2.5 mL, 5 mL, 7.5 mL
  • Devices: dosing cup, 0.5 mL increment or 0.2 mL increment oral syringes
• Error defined as > 20% deviation; large error > 2 x intended dose

Label and Dosing Tool Pairs

<table>
<thead>
<tr>
<th>Arm</th>
<th>Label Units</th>
<th>Dosing Tool Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>mL</td>
<td>mL</td>
</tr>
<tr>
<td>2</td>
<td>mL and tsp</td>
<td>mL and tsp</td>
</tr>
<tr>
<td>3</td>
<td>mL and teaspoon</td>
<td>mL and tsp</td>
</tr>
<tr>
<td>4</td>
<td>mL</td>
<td>mL and tsp</td>
</tr>
<tr>
<td>5</td>
<td>teaspoon</td>
<td>mL and tsp</td>
</tr>
</tbody>
</table>

* Considered gold standard

Yin et. al. Results

• 84.4% made at least 1 dosing error
• 21% made at least 1 large error
• Error rates among all arms ranged from 22.8% - 29.6%
• More errors with dosing cups (43%) than syringes (~ 16%) esp. with smaller doses (OR 4.6)
• Teaspoon-only labels resulted in more errors than milliliter-only label
• No statistical difference by health literacy though trend of more errors in low literacy group

Measuring Liquids Key Points

• No single fix. Milliliter only units current recommendation but may not be sufficient to prevent errors.
• For smaller doses, syringes appear best. Avoid household measures.
• RPh should think about appropriate device for product dispensed.
• Education and counseling key! Make sure caregiver has appropriate measuring device and knows how to use it. Teach back method best.
• Syringe cap adapter risks
  • Easily removed allowing access to medicine and choking hazard
  • Newer options available that are safer

Obesity

Definitions

• "Overweight" and "Obese" terms in adults based on statistical analysis of BMI and risk of morbidity and mortality
• No corollary in children
• BMI calculation same: BMI = Kg/m²
• "Normal" growth charts available from CDC (www.cdc.gov)
  • "Overweight" = > 85% to 95% normal BMI
  • "Obese" = > 95% normal BMI
• IBW* = 50th % weight for age or (height² x 1.65)/1000

* IBW in Kg, height in cm
Childhood Obesity in US*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 5 years</td>
<td>8.9%</td>
</tr>
<tr>
<td>6 – 11 years</td>
<td>17.5%</td>
</tr>
<tr>
<td>12 – 19 years</td>
<td>20.5%</td>
</tr>
</tbody>
</table>

Overall Prevalence = 17% or 12.7 million children

* Ogden et al. 2015

Johnson et. al.

- Retrospective review: 1 year of admissions at 2 large pediatric centers
- 18.8% of children age 2 to 17 admitted were obese
- On an average of 8 meds/admission
- Ranked top 25 meds prescribed
  - Analgesics, antimicrobials, corticosteroids, bronchodilators, GI meds
- Reviewed available PK data in obese children
  - 7 studies for 3 medications (cefazolin, midazolam, vancomycin)

Implications for Dosing in Children

- Very limited data available
- Be aware! Obtain and evaluate child’s weight.
- Use pediatric pharmacokinetic information if available
  - More clinical trials underway but usually exclude obese subjects
- Otherwise extrapolate from adult information if available
  - e.g. IBW for lithium, digoxin, theophylline and TBW for cephalosporins
- Do not exceed maximum adult dose
- Monitor serum levels or drug effects when possible to guide therapy

Key Points Obesity

- Childhood obesity on the rise
- Greater likelihood of having to evaluate dosing in an obese child
- Evaluate child’s weight
- Use specific data if available
- Extrapolate from adult data if necessary

Scenario

KM is a 6-year old boy with community acquired pneumonia. He weighs 26.4 Kg and is 118 cm tall. His pediatrician’s office has sent an electronic prescription for cefixime (Suprax) 200 mg/5mL oral suspension. Sig: Give 210 mg (5.25 mL) po daily x 10 days. In a respected pediatric dosing reference you find that the recommended dose is 8 mg/kg/day divided every 12 to 24 hours with a maximum daily dose of 400 mg.

Question 1

- What should KM’s weight be classified as?
  A. Underweight
  B. Normal for age
  C. Overweight
  D. Obese
Question 2

A. calibrated dropper
B. oral syringe
C. dosing cup
D. teaspoon

REFERENCES


Helpful Websites

- www.healthychildren.org
  - Consumer website of the American Academy of Pediatrics
- www.consumermedsafety.org
  - Consumer website of the Institute for Safe Medication Practices
- www.chpa-info.org
  - A member-based trade association of manufacturers/marketers of OTC products
- www.ppag.org
  - Pediatric Pharmacy Advocacy group.