Clinical Perspective: How Are We Doing From a Clinician’s Point of View

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Only half of meds taken by kids have 'adequate' safety info: study

Medications used in newborns especially under-studied, doctor says.

(HealthDay) -- About half of medications used in children have little or no label information about drug effectiveness, safety or dosing in children, new research finds.

"We still have a long way to go," said senior study author Dr. M. Dianne Murphy, director of the U.S. Food and Drug Administration's Office of Pediatric Therapeutics, although she acknowledged significant strides in pediatric labeling over the past few decades.

In the study, when the researchers looked at 560 medications listed in the 2009 electronic Physicians' Desk Reference, some not relevant for pediatric use, they found only 46 percent referred to children's usage. When they looked only at drugs used in children, they found "adequate" labeling information for 231 of 461 drugs. "Adequate" meant they included information on drug effectiveness, safety in kids and teens, and guidance on dosing.

Among medical professionals, there's a growing understanding that children aren't mini-adults. They may metabolize drugs differently, their bodies may react to drugs differently, and diseases themselves may have different causes or underlying mechanisms in kids than adults.

Dr. Daniel Frattarelli, a pediatrician in Dearborn, Mich., and chair of the American Academy of Pediatrics Drug Committee, said the numbers represent a big improvement over recent history. But 90 percent of medications used to treat newborns still have not been adequately studied, he said.

"We still have a huge problem with newborns," he said.

"It's great that we've made all of this progress in older children, but for babies, they're very vulnerable, they're often in the neonatal ICU [intensive care unit], and their metabolism is different even than for older children," Frattarelli said.
Safer Drugs for Kids

Many of the medicines children take have never been proven safe and effective for them. A new law will help change that.

Parents assume that when a pediatrician prescribes a drug for their child, that drug has been tested and proven safe and effective. If only it were so. Only half of the medicines doctors prescribe to patients 18 and younger have been through the same rigorous trials as those drugs prescribed to adults. The other half are given off-label—that is, in circumstances for which they were never properly vetted, putting children at risk for overdoses, side effects and long-term health problems. For newborns, that fraction rises to 90 percent. In July the U.S. Congress gave the Food and Drug Administration new authority to compel companies to test their products for kids. The law should improve the situation, but it has worrying gaps.
Children continue to be underrepresented in drug trials

July 23, 2012 in Pediatrics

(HealthDay) -- Even for conditions with a high pediatric disease burden, only a small proportion of clinical drug trials study pediatric patients, according to research published online July 23 in Pediatrics.

The researchers found that, for the selected conditions, 59.9 percent of the disease burden was seen in children, but only 292 of 2,440 trials (12.0 percent) were for pediatric patients (P < 0.001). Trials conducted without industry funding were significantly more common in pediatric populations compared with adults (58.6 versus 35.0 percent). Pediatric randomized trials were significantly less likely to examine safety outcomes compared with adult randomized trials (10.1 versus 16.9 percent) and had a modestly higher probability of publication in the examined time frame (32.8 versus 23.2 percent; P = 0.04).

"There is substantial discrepancy between pediatric burden of disease and the amount of clinical trial research devoted to pediatric populations," the authors write. "This may be related in part to trial funding, with pediatric trials relying primarily on government and nonprofit organizations."
Efforts to Improve Research on Kids' Drugs Paying Off: Report
But information still limited on long-term safety, efficacy, especially for infants

WEDNESDAY, Feb. 29 (HealthDay News) -- Federal laws requiring medical companies to conduct pediatric drug studies have helped provide guidance on whether it's safe or effective for children to use certain medications, a new U.S. report finds.

The Institute of Medicine (IOM) report noted, however, that there's still not enough data on the use of drugs in newborns or the long-term effects of drugs on kids generally. The IOM, part of the National Academies, is an independent, nonprofit organization that provides advice to U.S. policymakers, health professionals, industry and the public.

The report, released Feb. 29, concluded that Congress and the FDA could step in to improve research in these areas and force drug manufacturers to conduct timely long-term studies on the risk of medications among children or face penalties. This may be necessary, the report authors suggested in a news release from the National Academy of Sciences, because conducting research on children is more difficult and often yields less lucrative results than studies involving adults.

A Lack of Safety Data on Kids' Drugs Puts Pediatricians in a Bind
Few medications have been proved safe for children, leaving doctors in a bind
By Malinda Wenner Moyer

It is a conundrum that has frustrated pediatricians for decades: children get sick and need drugs, yet few medications have been approved for their use. A recent study and a government report published in February concluded that, most of the time, doctors are forced to prescribe drugs to young patients without adequate data, putting kids at risk for overdoses, side effects and long-term health problems. In late June Congress was poised to strengthen existing laws that encourage pharmaceutical companies to test medicines in kids, but that won't solve the safety problems associated with pediatric drugs.
Safe and Effective Medicines for Children
Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act

Pediatric drug studies remain particularly limited in certain areas, including the use of medications with neonates (infants younger than 28 days), and the long-term safety and effectiveness of medications used by children of all ages. The lack of information about the long-term safety of drugs prescribed for children is a special worry—both for drugs that may be used for decades for chronic conditions and for drugs for which short-term use may be found to harm children’s growth and development months or years later. Many medicines commonly used for premature and sick neonates are older drugs that have not been adequately evaluated in these vulnerable children.

Future Options for Improvement

The committee was not asked to make recommendations to the FDA, except with respect to pediatric studies of biologics. However, the committee did offer possible guidance in several areas. These include suggestions to:

- Address areas of limited pediatric investigation under BPCA and PREA, including studies in neonates and long-term safety studies. Congress can expand the BPCA program at the National Institutes of Health to include assessment of more drugs not adequately studied in newborns, and the FDA can use its authority to require long-term pediatric studies of serious safety risks.
The number of clinical trials enrolling children is far lower than for adults, and the scope of research is also narrower, according to an analysis of public-access data conducted by researchers at Duke University.
**Stages in the Course of Pediatric Ventricular Dysfunction**

- **Preventive Strategies:** Progressively less effective as the number increases.
  - Primary prevention is possible at number 1.
  - Secondary prevention is possible at numbers 2, 3, and 4.

- **Treatment Strategies:** Greater impact with higher numbers but longer effects with lower numbers.
  - Treatment is possible at numbers 4 and 5 to reduce sequelae.

- **Biomarkers/Surrogate Endpoints:**
  - Potentially more useful with lower numbers for alteration of course with interventions.
  - Potentially more useful with higher numbers for decisions about transplantation.

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Lipshultz et al., Prog Pediatric Cardiol 2000
Doxorubicin-Treated Survivors of Childhood ALL (Average Age at Exposure = 4 Years Old)

>12 papers said that early post-therapy dilated cardiomyopathy was reversible in the first few years after discontinuation of therapy

Lipshultz et al., JCO 2005
DFCI Childhood ALL Cohort: LV Contractility (Health of Heart Muscle Cells)

Long-Term Follow-Up is Essential to See if an Early Doxorubicin “Hit” Results in Late Cardiotoxicity Associated with Progressive Cardiovascular Morbidity and Mortality

- >12 million US cancer survivors – 1:640
- >50% anthracycline exposed

20-year Survivors
- >8-fold increased CV mortality
- >4-fold increased sudden death
- 10-fold increased atherosclerosis
- 5-fold increased myocardial infarction
- ↑ CV mortality from 15 to 25 yrs after Dox

30-year Survivors
- >3-fold increased anthracycline – associated CV mortality
- 15-fold higher rates of heart failure
- 10-fold higher rate of other CV disease
- 9-fold higher rate of stroke

Lipshultz et al., JCO 2001
Moller et al., JCO 2001
Lipshultz et al., NEJM 1991
Lipshultz et al., JCO 2005
Reulen et al., JAMA 2010
Mertens et al., JCO 2001
Mulrooney et al., BMJ 2009
Armstrong et al., JCO 2009
Lipshultz et al., NEJM 1995
Oeffinger et al., NEJM 2006

Dashed lines are the upper and lower 95% CI from the predicted mean +/- 2 SE of the mean.
CCSS: CHF Risk Increases with Anthracycline Dose

P for trend < .001

Netherlands: CHF Risk Increases Over Time

Blanco, et al., J Clin Oncol 2012

Van der Pal, et al., J Clin Oncol 2012
Estimates of (A) cumulative cardiovascular and (B) cardiac mortality in the French-British cohort and expected in the general population in France and Great Britain.
Cardiotoxicity 8-Years After Anthracycline Treatment of Childhood Cancer

LV Fractional Shortening (Heart Function)

Contractility (Health of Heart Muscle)
- Female Sex
- Cumul. Dose
- Age at Diagnosis
- Years Since Treatment
- Individual Dose

Afterload (Stress on Wall of the Heart)
- LV Wall Thickness
- LV Dimension

Cardiotoxicity 8-Years After Anthracycline Treatment of Childhood Cancer
Gender Difference

Probability of late decreased contractility 8 years after childhood cancer

Lipshultz et al., NEJM 1995
NCI DFCI: Effect of enalapril in delaying progression of depressed LVFS in long-term survivors of childhood cancer – 6-10 yrs of benefit
NCI DFCI Protocol 91-01: Continuous Doxorubicin Infusion is not Cardioprotective

LV Fractional Shortening Adjusted for Age

LV Posterior Wall Thickness Adjusted for BSA

LV Mass Adjusted for BSA

LV End-Systolic Dimension Adjusted for BSA

* p-value for diff bet treatment groups; † p<0.01 for diff bet baseline and follow-up time point
COMMENTSARY

The relevance of information generated by *in vitro* experimental models to clinical doxorubicin cardiotoxicity

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Mechanism of Doxorubicin Cardiotoxicity

Free Radicals
- Quinone-Semiquinone Recycling
- Dox-Iron Recycling
↓ Antioxidant enzymes
↓ Thiol Groups
↑ Oxidative stress

Subcellular Changes

Doxorubicin

DNA Intercalation
DNA-Topo II – Dox Complex
Impairs DNA replication

Anti-tumor Effects

Cardiomyopathy
Congestive heart failure
Light micrographs showing protective effect of dexrazoxane against DOX-induced cardiac lesions. Toluidine stain, x 400. Myocardial vacuolization and myofibrillar loss are less severe in rats treated with dexrazoxane/DOX 12 mg/kg (C) and dexrazoxane/DOX 7 mg/kg (D) than in rats treated with 12 mg/kg DOX (A) or 7 mg/kg DOX (B) alone.

Herman, Lipshultz, et al., JCO 1999
NCI DFCI 9501 Cohort: Dexrazoxane Reduces Myocardial Injury

Day of doxorubicin treatment
- Doxorubicin
- Dexrazoxane/Doxorubicin

Lipshultz et al., NEJM 2004
NCI DFCI ALL 9501 Cohort: Doxorubicin-Treated Children – Girls are Cardioprotected by Dexrazoxane

Left ventricular end systolic dimension

Girls

Boys

Left ventricular fractional shortening

Girls

Boys

Left ventricular end diastolic posterior wall thickness

Girls

Boys

Lipshultz et al., Lancet Oncol 2010
Ventricular Remodeling in Systolic and Diastolic Heart Failure as a Function of Time

McMurray, Pfeffer, Heart Failure Updates 2003

NCI DFCI ALL 9501 Cohort: Left Ventricular Thickness to Dimension Ratio in Doxorubicin-Treated Children; Dexrazoxane Blocks LV Remodeling

Lipshultz et al., Lancet Oncol 2010
Abnormal NT-proBNP (Cardiomyopathy, Age >1 yr ≥ 100 pg/mL; Age < 1yr abnormal ≥ 150 pg/ml) during doxorubicin therapy is not significantly related to lower left ventricular mass, wall thickness, and remodeling but is related to LV remodeling (thickness to dimension ratio) by echo 4 years later.

Myocardial injury (measurable serum cardiac troponin T, ≥ 0.01 ng/ml) during doxorubicin therapy is significantly related to lower left ventricular mass, wall thickness, and remodeling by echo more than 5 years later.

Lipshultz et al., JCO 2012
Second Study: NCI COG 9404 T-ALL: Dexrazoxane is Cardioprotective 3 Years After Doxorubicin

LV Fractional Shortening

LV Wall Thickness

LV Thickness-to-Dimension Ratio (LV Remodeling)

†p-value for difference between groups

‡p-value for differences in change of mean z-scores between groups

Asselin, Lipshultz, ASCO 2012
Third Study: Dexrazoxane is Cardioprotective for Additive Cardiotoxicity
NCI COG AOST 0121

Herceptin/Dox Additive Cardiotoxicity Protected by Dexrazoxane

No Cardiomyopathy by NT-proBNP with Dexrazoxane

Both Groups Not Significantly Different from Normal

Both Groups Below the Cardiomyopathy Threshold

Kopp, Lipshultz, ASCO 2012
Ebb, Lipshultz, JCO 2012
Fourth Study: Dexrazoxane is Cardioprotective with Doxorubicin Dose Escalation: NCI COG P9754: No Fall in LVFS slope going from 450 to 600 mg/m² of Doxorubicin when Dexrazoxane is used

Both Groups Not Significantly Different from Normal

Kopp, Lipshultz, ASCO 2012
**Increased Confirmed Mutations or Polymorphisms in mtDNA of Peripheral Blood Lymphocytes in 10-year ALL Survivors**

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*Potentially pathologic; ♦polymorphism; * Both

**NCI DFCI 05-336 Mitochondrial Structure and Function in 10-year ALL Survivors**

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<th>Variable</th>
<th>N</th>
<th>DOX Median (range)</th>
<th>N</th>
<th>DOX/DEX Median (range)</th>
<th>P</th>
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<td>mtDNA copies/cell</td>
<td>27</td>
<td>1106.3 (144.2-8746.8)</td>
<td>35</td>
<td>310.5 (15.3-1859.2)</td>
<td>0.001</td>
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<td>CI Activity (OD/mg x 10&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>25</td>
<td>10.5 (5.0-31.3)</td>
<td>33</td>
<td>11.7 (5.0-41.4)</td>
<td>0.97</td>
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<tr>
<td>CIV Activity (OD/mg x 10&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>25</td>
<td>9.8 (5.0-20.1)</td>
<td>34</td>
<td>8.1 (4.7-23.4)</td>
<td>0.40</td>
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</table>

**Results:** Significantly higher number of mtDNA copies in DOX group compared to DOX/DEX group

- mtDNA = mitochondrial DNA copies/cell
- CI = oxidative phosphorylation (OXPHOS) NADH dehydrogenase activity
- CIV = oxidative phosphorylation (OXPHOS) cytochrome c oxidase activity
- OD = Optical Density

**Cancer survivors (n = 167):**
64 sequence variants identified in 51 of 167 patients screened
(avg = 0.31 sequence variants/patient; 30% of patients ≥ 1 change)

**Healthy controls (n = 56):**
8 sequence variants in 7 of 56 patients (avg = 0.14 sequence variants/patient;
12.5% patients ≥ 1 change, p = 0.008)

Lipshultz, ASCO 2010
Lipshultz, ASCO 2012
Hemochromatosis Gene Mutations

Miranda et al. found that the heterozygous HFE knockout mice (Hfe+/-) showed mitochondrial degradation and increased mortality as compared to wild-type mice after chronic doxorubicin exposure.

Wild type

Hfe +/-

Miranda, et al., Blood 2003
C282Y mutations were significantly associated with 8-fold increased risk of elevations in cTnT

<table>
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<th>Biomarkers</th>
<th>OR*</th>
<th>95% CI</th>
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<td>abnormal NT-proBNP</td>
<td>1.49</td>
<td>0.31-7.19</td>
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• OR: Odds Ratio
• Abnormal cTnT: >0.01ng/ml;
• Abnormal NT-proBNP: ≥150 pg/mL in infants younger than 1 year or ≥100 pg/mL in children aged 1 year or older

* Adjusted for dexrazoxane

LV Characteristics by HFE Carrier 2 years after Randomization

Carriers showed more dilated left ventricles, LV dysfunction, thinner posterior wall thickness, and reduced LV mass than normal

Lipshultz, ASCO 2011
Anthracycline Summary

- Cardiotoxicity associated with cancer therapeutics can be pervasive, persistent, and progressive but missed clinically
- If you don’t look, you don’t know
- Tailored follow-up and therapies are needed and may be unique
- Genetic, environmental, and temporal factors interact to cause toxicity and identify high risk groups for safer treatment options and targeted interventions
- Validated surrogate cardiac endpoints are lacking
- Survivor cardiac monitoring delays heart failure and improves QOL
- Enalapril delays but does not prevent progressive survivor cardiotoxicity
- Continuous infusion doxorubicin is not cardioprotective
- Dexrazoxane is cardioprotective and allows safe dose escalation and the use of additive cardiotoxic therapies
- Persistent mitochondrial damage may relate to lifespan cardiotoxicity
The relevance of information generated by in vitro experimental models to clinical doxorubicin cardiotoxicity.

Myocardial injury and other markers and cardiac function are often not concurrently evaluated.

What is called contractility as a measurement is often more than an assessment of intrinsic myocardioocyte health. Usually it is load-dependent incorporating preload, afterload, and heart rate.

No common definition of drug-induced cardiotoxicity has been established.
- Long-term animal models are lacking.
- Few cardiac biomarkers have been validated as surrogate endpoints for clinically important cardiovascular disease.
- Cardiovascular regulatory toxicology vs. non-regulatory safety pharmacology endpoints – When used for discovery and drug development without understanding or a priori agreements are likely to be stultifying to development and have consequences.
- HR, BP, and ECG are rarely clinically meaningful as toxicology or safety endpoints clinically for lifespan toxicity vs. efficacy evaluations of a new agent.
- Understanding the course of pharmacodynamic properties, pathophysiological effects and mechanisms of adverse effects of a new agent are critical in lifespan toxicity vs. efficacy evaluations.