Chapter 53 - What are the requirements for medications in children?
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Children and adolescents get many of the same diseases as adults and, by necessity, are often treated with the same medications. Yet the American Academy of Pediatrics estimates that only a small fraction of all drugs marketed in the U.S. have been studied in pediatric patients, and a majority of marketed drugs are not labeled – or are insufficiently labeled – with directions for use in pediatric patients.

_Why do young children differ from adults?_
Children are not just small adults. Their uptake, breakdown and excretion of medications may be limited at birth, but improve during the first year of life. At birth, infants lack certain essential enzymes in the liver, the primary site of breakdown. Moreover, medications are excreted more slowly through the kidneys – the main route of medication elimination in young children – but the kidney function improves during the first year of life and may even exceed that of adults. Finally, body composition also differs between children and adults. For example, the water content in a newborn child is 70 percent, compared to 55 to 60 percent in adults. This may affect the dosing of water-soluble medications.

_In the absence of clinical trials, how is medication dosing determined?_
The dosing of medications in children and adolescents often takes place with no clinical trials to guide the prescriber. One important option in this situation is to review the medical literature to see if other prescribers have reported the use and dosage amount of the medication in younger patients. This type of evidence is not as good as a clinical trial, though, and failures with the medication may not be reported in medical journals.

If there are no clinical trials or reports in medical journals and the medication absolutely must be given, then it is left to a highly educated guess. By taking into account how the drug is absorbed, distributed, broken down, and eliminated in adults, hopefully a safe and effective dose can be found for a child or adolescent.
What are the concerns?
Medications are not routinely tested in children or adolescents before being cleared for marketing by the FDA. The absence of testing poses significant risks for these age groups; for example, inadequate dosing information exposes younger patients to the risk of adverse reactions.

Treating children with various medications continues to create risks to them. In January 2008, the FDA issued a Public Health Advisory warning about nonprescription cough and cold medicines, indicating these should not be given to infants and children younger than 2 years of age. The safety and effectiveness of these products are unknown, as these medications were not studied in this age group. The agency had received reports of convulsions, rapid heart rates, decreased levels of consciousness, and death with the use of these products in children younger than 2.

Because of limited clinical trials, much of what is known about the adverse effects of medications in infants and children comes from the FDA Adverse Event Reporting System (AERS), which provides voluntary reports of problems made by health professionals and consumers to medication manufacturers and the FDA. Between 1998 and through 2005, the number of serious adverse drug reactions reported to the FDA increased by 2.6-fold. During the same period of time, reports of fatal adverse drug events multiplied 2.7-fold.

Serious adverse events occur less frequently in children and teenagers than in adults, but the number of occurrences increased rapidly between 1998 and 2005. The top six medications which accounted for 20 percent of all serious injuries are not indicated or recommended for treatment of serious medical illnesses. Examples include a treatment for severe acne, an antidepressant found ineffective in children, a hormone to increase stature, and treatments for attention deficit hyperactivity disorder. Research published in 2002 indicated that between November 1997 and December 2000, 769 deaths reported to the FDA were associated with the use of medications in infants and children younger than 2.

What actions need to be taken to improve the documentation in children?
Congress recognized in the early part of this decade that pediatricians and parents did not have sufficient information about the safety, effectiveness and dosage of medications to make informed decisions about how to use them, or whether they should be given to a child.

To close this information gap, Congress passed the Best Pharmaceuticals for Children Act (BPCA) of 2002 and the Pediatric Research Equity Act (PREA). Both laws were designed to encourage more research into children’s medication use. The BPCA gives the pharmaceutical industry a
significant financial incentive to conduct research in children with medications the FDA already approved for the treatment of adults. Companies which do the research with their older medications in children are granted an extra six months of market exclusivity – in other words, it is similar to extending the patent on the medication for six more months. Even a drug with modest sales can gross $1 million per day on the market, making this incentive very important to a company’s bottom line.

Exclusivity is granted to manufacturers whether or not the results of the research found the medication safe and effective in younger populations. In some cases, manufacturers may have conducted studies in children with medications that have little or no chance of being used in younger age groups just because of the exclusivity benefit. Overall, however, the BPCA must be considered a success because there is now safety, effectiveness, and dosing information for children and adolescents based on clinical studies available for about 200 drugs.

Key messages

✔ Children, particularly those younger than 2, handle medications differently.
✔ Drug dosing in children should to be determined in clinical studies, but there are currently a limited number of these studies.
✔ In the absence of clinical trials, the dose for children is typically the adult dose adjusted for body weight and other factors.
✔ Children may suffer serious adverse reactions due to improper dosing.
✔ Congress has taken steps to improve the documentation of medications in children.