JPPT

YAFFE AWARD LECTURE

Pediatric Pharmacology: Its Time Has Come

Sumner J. Yaffe, MD

Visiting Professor, Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, California

Keywords: pediatrics, pharmacology, federal regulations

Editors note: The Pediatric Pharmacy Advocacy Group awarded Sumner J. Yaffe the first annual Yaffe Lifetime Achievement Award in Pediatric Pharmacology and Therapetics on October 2, 2002 at their annual meeting held in St. Petersburg, Florida. Below are his remarks to the organization.

In 1607 Voltaire wrote, "Doctors pour drugs of which they know little, to cure diseases of which they know less, into patients of whom they know nothing". Unfortunately, this is still relevant today and is particularly applicable to pediatric therapeutics. Throughout the past century, pediatric drug therapy has played a major role in modifying the climate for clinical pharmacology in the United States and throughout the world. Unfortunately, several therapeutics misadventures in infants and children occurred before appropriate pediatric regulatory changes in the Food and Drug laws of this country took place and, by extension, to those regulations of the western world.

The first pivotal misadventure associated with drug use occurred at the beginning of the last century, when 14 children developed tetanus following administration of diphtheria antitoxin. Although the St. Louis Board of Health had prepared the antitoxin, it was derived, unfortunately, from a horse that was infected with tetanus. This occurrence led to the congressional enactment of the Biological Control Act of 1902, which ensured the purity and safety of biological products (i.e., serums and vaccines) used to prevent or treat disease in humans. This led to the Federal Food and Drug Act of 1906, which addressed the interstate transport of adulterated or misbranded foods and drugs. Unfortunately, this act did not obligate the manufacturer to insure the efficacy and safety of the drug.

In 1937, one of the first effective antibacterial drugs, sulfanilamide, was developed as a pediatric formulation to treat gram positive infections, primarily streptococcal, in children. To dissolve the insoluble sulfanilamide, diethylene glycol was selected as the solvent, and raspberry syrup was added for taste. Two-hundred and forty gallons of the elixir were distributed between September 4 and October 15, 1937. While diethylene glycol was an excellent solvent, it proved to be highly toxic, causing renal failure and subsequent death of 107 children who took the solution of sulfanilamide. The deaths were not in vain, for they prompted Congress in 1938 to amend the Food and Drug Cosmetic Act. The amended act required safety of the drug and truthful labeling of a product's composition . Toxicity studies and approval of a new drug application (NDA) were required before a drug could be promoted and marketed.

In this minimally regulated environment, research in basic and clinical pharmacology proliferated in both industry and academia. Many new drugs were developed and brought to market, but without rigorous proof of efficacy, therapeutic claims could not be validated by objective data. This resulted in extravagant claims regarding therapeutic indication, which were commonly made. As a result, the benefit to risk ratio was poorly defined and seldom mentioned when a drug was brought to market.

All of this changed radically in the early 1960's, when a new hypnotic-sedative with a short half-life, Thalidomide, was introduced in Europe, Australia and Canada. After several

Address correspondence and reprint request to Sumner J. Yaffe, MD, Department of Pediatrics, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Room B2-375 MDCC Los Angeles, California 90095-2753; e-mail: sjyla@aol.com

years, it became dramatically apparent that the occurrence of a rare, but strikingly obvious, anatomic birth defect, phocomelia, was increasing markedly. The birth defect soon reached epidemic proportions, and retrospective epidemiological research firmly established the etiologic agent to be Thalidomide that was prescribed during the first trimester of pregnancy.

Although the drug had not been approved by FDA for marketing in the United States, the U.S. Congress reacted quickly by passing the Harris-Kefauver amendments to the Food and Drug and Cosmetic Act in 1962, another example of a tragedy in pediatrics which prompted drug regulatory changes.

These amendments, which form the basis of today's FDA, are well known. The amendments require sufficient pharmacological and toxicological research in animals, submitted in the form of an investigational new drug application (IND) before clinical studies can begin. In order to demonstrate efficacy, adequate and well-controlled clinical trials must be performed. It is important to note that manufacturers were required to also provide data to support the claims of efficacy for all drugs marketed between 1938 and 1962. Safety must be demonstrated by having a sufficiently large database so that the benefit-versus-risk ratio can be determined.While the 1962 amendments represented a significant advance in drug regulation and hence a great improvement in the quality of drugs available to the U.S. public, they brought dire consequences to drugs available for children.

Even though children comprise more than a third of the population, their generally healthy status provided little economic incentive for the pharmaceutical industry to develop and study drugs in the pediatric population. As a consequence, only one in five drugs prescribed for children has ever been evaluated in this population. Thus, a culture of off-labeled usage of medications developed. As a result of this climate, Dr. Harry Shirkey wrote, "By an odd unfortunate twist of fate, children are becoming therapeutic pharmaceutical orphans."

Table. PPRU Network Goals 1999-2004

- Performance of drug trials leading to labeling
- Advancing of clinical trials methodology in pediatrics: pharmacokinetic-pharmacodynamic, developmental and validation of surrogate and biomarker endpoints
- Provision of training in pediatric clinical pharmacology and clinical trials methodology
- Performance of translational research; ontogeny of drug metabolizing enzymes, receptors, transporters, and ion channels
- Provision of consultation to pharmaceutical companies in clinical trials design

The academic pediatric community reacted by convening several conferences to discuss the problem and its possible solution. In 1967, the U.S. Department of Health Education and Welfare held a conference in Washington D.C. Sponsorship included the FDA, the National Academy of Sciences, and The National Institutes of Health. The conference recommended""drug testing in minors" and suggested that research be undertaken to determine how to best accomplish this testing; however, no realistic solutions were developed.

In 1968, Ross Products Division Abbott Laboratories, Inc., well known for its sponsorship of conferences on pediatric research, held a symposium on problems of drug evaluation in infants and children. Again, no practical solutions were offered, but attendees discussed the lack of funds for research and research training in pediatric pharmacology.

In 1974 the Committee of Drugs of the American Academy of Pediatrics produced a report for FDA, which provided general guidelines for the evaluation of drugs in this special population. The report was incorporated by FDA into their general guidelines in 1977. Surveys conducted at that time and in the early 1990's revealed that little progress had been made to resolve the therapeutic orphan state of affairs in this country.

In 1990, the Forum on Drug Development of the Institute of Medicine sponsored a workshop to address the lack of pediatric labeling. Key players in the workshop were FDA, the NIH (NICHD), the pharmaceutical industry and academia. Recommendations were made to all the parties involved in the workshop.

FDA was petitioned to facilitate pediatric labeling by allowing extrapolation from adult studies, provided the course of the disease was similar in adults and children and to provide economic incentives by extending patent exclusivity. The NIH was asked to provide the requisite infrastructure for collaborative studies, and the pharmaceutical industry was asked to take a more proactive stance in conducting drug studies in infants and children. In response to a recommendation from the Institute of Medicine,

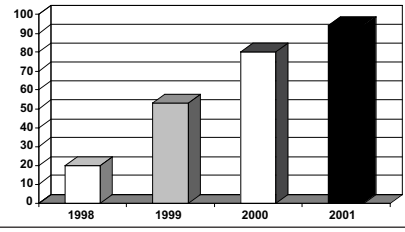
FDA published the pediatric rule of 1994, which had minimal voluntary response from industry. Following an endorsement by its advisory council, the NIH established the Pediatric Pharmacology Research Unit (PPRU) network in 1994. A competitive RFA resulted in a PPRU network that consisted of seven academic institutions. Each unit was headed by a qualified pediatric clinical pharmacologist. The network's first challenge was to demonstrate whether or not comprehensive labeling studies could be performed in these seven sites in cooperation with the pharmaceutical industry. The PPRU was also presented with additional directives (Table).

In the ensuing 5 years, the network performed over 100 studies that involved more than 1000 newborns, infants, children, and adolescent patients (FIGURE). This demonstrable success prompted NICHD to expand the network to 13 sites located throughout the U.S. Each unit possessed a large and adverse pediatric population that collectively included 160,000 in-patient admissions/year, over 2,000,000 out-patient visits/year, and ~ 28,000 NICU admissions/year.

In the meantime, FDA published the final rule of 1998, which was not to become effective until 2000. This rule empowered FDA to "insure that new drugs and biological products that are likely to be commonly used in children or that represent a meaningful therapeutic benefit over existing treatments for children contain adequate pediatric labeling." The rule dealt with original applications of drugs classified as "new chemical agent" and some drugs that had already been marketed. The rule also included neonates and required pharmaceutical manufacturing of pediatric formulations. On March 18 of 2002, FDA postponed implementation of the rule for an additional 2years. Following overwhelming criticism, FDA moved to restore the rule.

At the same time, Congress enacted the Food and Drug Modernization Act (FDAMA) of 1997, which under section 111, provided 6 months of patent exclusivity in exchange for pediatric studies. FDAMA produced a striking increase in studies in infants and children with 37 label changes, 293 pediatric study requests from industry and 237written requests issued by the FDA. There was more activity in two years than in the previous three decades. FDAMA had an impact upon the PPRU with a marked increase in the number of protocols prepared (Figure).

Figure. Peditatric Pharmacology Research Unit (PPRU) clinical investigations 1998-2001



More recently (January 2002), Congress passed the Best Pharmaceuticals for Children Act (sponsored by Senators Dodd & Dewine). This act not only extended the exclusivity provisions of FDAMA, but also established an office of pediatric therapeutics at FDA. The Act authorized $200 million per year for the study of off-patent drugs and required the NIH to develop a priority list of such drugs. It also created a pediatric advisory committee at FDA and established a foundation for pediatric research at NIH to fund pediatric research studies. With this act, pediatric pharmacology has at long last come of age!

Finally, I would like to quote from Sir William Osler, who in 1889 said "The century opened auspiciously and those who were awake, saw signs of the dawn." For those who are visionary, let us project some thoughts regarding future directions and need.

With the explosion in molecular biology, we must apply these techniques to developmental pharmacology. Much is to be gained by applying a developmental approach to gene expression, pharmacogenomics and the development of drug receptors, and cellular mechanisms for drug uptake and distribution. It is also important to elucidate the molecular mechanisms underlying changes in DME activities during development.

Clinically, many off-patent drugs require study; however, the pharmaceutical industry has little interest in validating these clinical efficacy, phramacokinetics, or side effects of these agents in the pediatric population. The neonate is exposed to a large number of drugs for which there is little scientific information. This need is highlighted in the Best Pharmaceuticals act for Children, mentioned above. Pediatric formulations are in need of development as well as data regarding fetal therapy. To accomplish all of this, training of scientists qualified to pursue these investigations must be supported.