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Pharmacological research in pediatrics: From neonates to adolescents ☆

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Abstract

The data guiding the dosing, efficacy and safety of medicines for children have lagged substantially as compared to the information available for adults. As a consequence, pediatricians faced with the prospect of confining their practice to medicines with adequate information have frequently resorted to prescribing medicines for unapproved uses (different dose, frequency, age group, route, indication or formulation). Although a long time in coming, the past decade, have witnessed a new era in drug development for children — an era that is still in its infancy, but which is currently showing signs of maturation. This review will give some of the history and current progress in pharmacological research and pediatric drug development.

Keywords: Drug therapy in pediatrics; Off-label prescriptions; Drug metabolism in pediatrics; Phase I enzymes; Phase II enzymes

Contents

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1. History

The history of drug therapy is replete with examples of adverse reactions to drugs in neonates, infants, children and adolescents. In 1937, 107 people–primarily children–died after taking elixir of sulphanilamide to treat streptococcal infection. Sulphanilamide was not very water soluble, but a chemist at Massengill Co. found that it dissolved well in diethylene glycol (more commonly known as antifreeze), which is now known to be highly toxic. In 1956, Andersen et al. at Columbia reported an excessive mortality rate and an increased incidence of kernicterus among premature babies receiving a sulfonamide antibiotic compared with those receiving chlortetracycline [1]. Then, in 1959, Sutherland described a syndrome of cardiovascular collapse in three newborns receiving high doses of chloramphenicol for presumed infections [2]. More recently, the therapeutic misadventures experienced by low birth weight infants exposed to a parenteral vitamin E formulation [3] and the "gasping syndrome" by infants who received excessive amount of benzyl alcohol [4] all serve to underscore the generally held perception that newborn infants are more likely to experience adverse reactions to drugs. More recently, all therapeutic issues surrounding the retinoic acid embryopathy and maternal antidepressant drug use have refocused attention on the effects of drugs on the fetus and newborn [5].

As a result of these experiences, pediatricians have become extremely conservative in their use of drug therapy. Although this conservative approach has permitted the fulfillment of the physician's oath to "do no harm," it also has prevented the adoption of newer therapeutic modalities and their adaptation to neonatal patients.

A more specific approach to pediatric therapeutics that will improve the safe use of medicines in this population requires a thorough understanding of human developmental biology as well as insights regarding the dynamic ontogeny of the processes of drug absorption, drug distribution, drug metabolism, and drug excretion. In addition, there must be a rigorous appreciation of the developmental aspects of drug-receptor interactions, including the ontogenetic changes in receptor number, receptor affinity, receptor–effector coupling, and receptor modulation and regulation.

2. Off-label prescribing

At intervals since 1968, surveys have documented that only a minority of medicines receive labelling for pediatric use. Even fewer receive labelling for use by neonates and infants [6]. In the period 1973–1997, the percentage of approved drugs that contained no labelling information for children remained fairly stable at 71–81% [6]. Of the 33 new molecular entities (NMEs) approved in 1997, 27 had potential for pediatric use, but only nine contained any pediatric labelling information.

With so few medicines containing adequate labelling information to guide their use, off-label prescribing became an accepted practice. Off-label prescribing includes the use of drugs for unapproved indications, or a different age group, dosage, frequency or route of administration. It also includes the administration of