Adverse Drug Reactions in Children: Pediatric Pharmacy and Drug Safety

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An underappreciated problem in child health is the risk for adverse drug reactions (ADRs). While there is an impression that children are at a lower risk than adults for ADRs, in fact a number of factors germane to pediatric therapy place certain groups of children at a high risk for adverse events associated with therapy. Given the importance of drug safety, an understanding of a diagnostic classification for ADRs and of how to approach a possible ADR clinically are key skills for pediatric pharmacists. As drug therapy for children evolves, becomes more complex, and begins to use novel molecules and biologicals there will be an increasing need for pediatric pharmacists to be more involved in clinical care, education, and research specific to drug safety.

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Introduction

Historically, childhood has been a very dangerous place to be. Until relatively recently children have had a very high likelihood of suffering serious illness, typically infectious, and death. An estimate is that children in ancient Egypt had a 30% chance of dying before puberty, while a similar estimate in the United States in the 19th century was 25%.¹ This unhappy statistic was changed by 3 major changes: the creation of vaccines, public sanitation, and the development of specific pharmacotherapy.

While discovery of specific therapy in the popular imagination is often linked with the discovery of the antibiotic activity of penicillin by Sir Alexander Fleming in 1928, in fact, the “Therapeutic Revolution” began in earnest with the observation that Prontosil—a derivative of azo dyes—was a potent antimicrobial agent.² While Fleming’s discovery was largely unexploited clinically for a decade, within 2 years of Gerhard Domagk’s work with Prontosil, sulfonamides were in routine clinical use. The impact was profound, as eloquently documented in Lewis Thomas’ outstanding book, *The Youngest Science*.³ Lewis Thomas, who was a “House Officer” in the Boston hospital system at the time that sulfonamides were first being widely used, noted that the impact of effective antimicrobial therapy was the approximate equivalent of what would happen today if we were able to cure cancer.³

However, nothing comes for free. Again, within 2 years of the discovery of its antimicrobial effect came the observation that sulfonamide therapy could be associated with serious adverse effects.⁴ Case reports were published describing the association of sulfonamide therapy with delayed adverse events—which today we would describe as “delayed hypersensitivity

reactions.”⁴ The more significant adverse event was the “Elixir of Sulfanilamide Tragedy” of 1937, in which more than 100 Americans—mostly children—died as a consequence of the use of diethylene glycol—a potent nephrotoxin—as a solvent for sulfanilamide.^{5,6} The preparation had not been tested for toxicity before being sold on the market. This tragedy shocked the nation and hastened the modernization of the Food and Drug Act of 1906; the subsequent Food and Drug Act of 1938 laid the foundations for the current drug regulatory process, in which requirements for safety and efficacy are clearly laid out. Sadly, the stimulus for this was the death of a number of children.

Subsequently further tragedies involving therapeutics and children have fueled further legislation, such as the Kefauver-Harris amendments to the Food and Drug Act, signed into law in response to the Thalidomide Tragedy in 1961.⁷ This legislation, which was intended to enhance safety of medication for children, had a paradoxical and indeed contrary effect.⁸ Shifting the balance of power in the regulatory approval process for new drug firmly to the side of Federal regulators created an environment in which it should have been relatively easy to ensure that drugs used for children were both effective and safe. In practice, the converse occurred.¹ When the legislation was considered in detail it became clear to the pharmaceutical industry that the regulations applied to product labeling.⁸ Consequently if a product was not labeled for a specific population, then efficacy and safety requirements, which in the 1960s were certainly more difficult to demonstrate for children than for adults, would not need to be studied or demonstrated. Thus, exclusionary language—“this drug is not labeled for use in patients under the age of 12”—became the norm. Despite this labeling, however, clinicians used new medications for the treatment of

Table 1. Risk Factors for Adverse Drug Reactions in Children*

History of a previous adverse drug reaction
Extremes of age
Impairment of liver or renal function
Polypharmacy
Female sex
Certain genetic polymorphisms
General anesthetic use
Off-label drug use

* Modified from Rieder¹⁶ and Gallagher et al.²⁸

children, frequently guided by experience rather than evidence. This situation, in which as many as 75% of prescription medications were not approved for use in children and in which off-label use was the norm, was starkly characterized by Shirkey, who described children as “The Therapeutic Orphan.”^{9–11} Over the past 2 decades, a number of initiatives have been undertaken to address this problem, both in the United States and Europe.^{12–14} While great progress has been made, many challenges remain in the provision of optimal drug therapy for children. One of the major challenges remains the issue of drug safety and adverse drug reactions (ADRs).

Adverse Drug Reactions in Children

There are a number of definitions for ADRs, but in essence an ADR indicates harm resulting from the use of a medication.^{15,16} The classical work of Lazarou and colleagues established that hospitalized patients had a significant risk of suffering an ADR, an observation confirmed by a number of subsequent studies.^{17,18} There has historically been an impression that children are at a lower risk of ADRs than adults.¹⁶ While the bulk of this work has been conducted among adults, there are a small but growing number of studies^{19–28} that demonstrate that children also have an appreciable risk for ADRs. One of the most comprehensive recent studies²⁶ has suggested that 3% of hospital admissions to a large British Children’s Hospital were due to ADRs.

The fact of a significant risk for ADRs in children is due in part to known risk factors and is in part due to the nature of pharmacotherapy for children.¹⁶ There are a number of known risk factors for ADRs (Table 1), many of which are clearly germane to therapy for children.^{16,26} When the nature of pharmacotherapy for children is considered, the groups of children most at high risk for ADRs become clear.

Pharmacotherapy in children is somewhat unique compared to that in adults in that there is a much less unitary distribution of therapy. The use of prescription medication among children is at first glance much more

Table 2. Classification of Adverse Drug Reactions*

Predictable	Unpredictable
Side effects	Intolerance
Secondary effects	Allergic/pseudoallergic
Interactions	Idiosyncratic
Toxicity	Psychogenic

* Modified from Rieder¹⁶ and Rawlins and Thompson.⁴⁴

common than might be expected; in a study²⁹ we conducted among a million Canadian children we found that over the course of a year there were 3.9 million prescriptions dispensed to these children. However, this did not translate into each child receiving 3 to 4 prescriptions per year. Rather, there was a large group of children (nearly 70%) who received either no medication or 1 prescription per year, frequently an antibiotic.²⁹ In contrast, a smaller group of children (roughly 20%) accounted for 70% of prescription drug use.²⁹ Other studies^{30–34} have confirmed this observation. These children belong to groups that one would predict: children with cancer, children with asthma, children with epilepsy and other chronic health problems, as well as children in the Neonatal Intensive Care Unit and in the Pediatric Critical Care Unit. In this light, when we consider the known risk factors for ADRs (Table 1), it is no surprise that these children are likely to be at risk for ADRs. Polypharmacy is common; many of these children have impairment in renal or kidney function, and many have sustained ADRs relative to the use of other drugs. When making treatment decisions, clinicians caring for these children need to be cognizant of the very real risk of ADRs.

In addition to the risk factors for ADRs and the nature of pediatric pharmacotherapy (predisposing certain groups of children to a high risk of ADRs), there are also some unique ADR patterns seen primarily in children. Developmental pharmacology studies^{35–39} have for many years focused on issues germane to newborns, notably preterm newborns. The appreciation of the ontogeny of drug-metabolizing enzymes, the maturation of renal function, and, more recently, our understanding of transporter development has been translated into changes in therapy—notably in dosing interval—that have made therapy of preterm infants safer and more effective.^{35–39} It has been somewhat less widely appreciated that there may be changes in other phases of childhood that place children at risk for ADRs, including ADRs that are appreciably different from those in adults. Examples include the risk of serum sickness-like reactions to cefaclor (1% in toddlers compared to 1:1000 for adults), the risk of valproic acid–induced hepatic injury (markedly more common in children under the age of 5 years than at other ages of life), and the risk of serious skin rashes related to the use of lamotrigine (age under 13 years being a risk factor).^{40–42}

The Clinical Approach to ADRs

When considering how to approach a possible ADR, an important consideration is how ADRs are classified. While there are several different diagnostic classification schemes used, one that is both widely used and practical is that of Rawlins and Thompson, which considers acute ADRs to be either “predictable” (Type A) or “unpredictable” (Type B) (Table 2).

Predictable ADRs are those that can be anticipated predicated on the known pharmacology of the drug. This ADR pattern is the most common type of ADR, and these ADRs tend to be less severe and often self-limited. Typical predictable ADRs include side effects—which are usually off-target effects such as hand tremor associated with inhaled albuterol—and secondary effects, such as pseudomembranous colitis due to lincosamide therapy.^{16,44} Other predictable ADRs include interactions, which may be drug-drug, drug-disease, or drug-food in nature. As noted above, the common use of polypharmacy among children with chronic disease makes an understanding of drug interactions very important for clinicians caring for children. Another type of predictable ADR is toxicity—simply put, too much of anything is harmful.

Unpredictable ADRs are those whose evolution, while possibly understood to some degree, is not predictable based on the drug’s known pharmacology.^{16,44} These are less common but often more severe. As an illustration, many fatal ADRs are unpredictable ADRs. Patterns of unpredictable ADRs include “intolerance,” in which vulnerable subsets of patients experience disabling adverse effects at usual doses (for example, disabling tinnitus during low-dose salicylate therapy), and “allergic/pseudoallergic reactions: (such as penicillin allergy). Idiosyncratic ADRs are often very severe, for example, Stevens-Johnson Syndrome associated with sulfonamide therapy or clozapine-associated agranulocytosis. A final and very difficult to manage unpredictable ADR pattern involves psychogenic ADRs, a type of adverse event that is difficult for clinicians and disabling for patients.

The clinical approach to a possible adverse event occurring as a consequence of drug therapy involves the “Five As” (Table 3).¹⁶ This is a stepwise approach that encourages a thoughtful and careful evaluation followed by management and follow-up. The first step—appreciation—is the understanding that an undesired effect may be the consequence of therapy. In the setting of therapy, patients and families often attribute undesired effects to medications, while clinicians often attribute them to the disorder being treated. While the truth is often somewhere in between, the clinician must have an open mind as to the possibility that the drug might be responsible.

The second step—assessment—involves careful data collection to ensure that all the elements of the

Table 3. The Five A’s—A Clinical Approach to a Possible Drug-Induced Adverse Event*

Appreciation
Assessment
Analysis
Assistance
Aftermath

* Modified from Rieder.¹⁶

undesired effect, as well as the disorder being treated and the characteristics of the patient being treated. The importance of a comprehensive assessment cannot be overstated, as the key information guiding the differential diagnosis is almost entirely clinical.

The next step—analysis—is one in which a reliable and informed drug information source is crucial. The analysis of the data gathered during assessment is designed to essentially determine if the event in question is drug-related or not. Given the large number of marketed therapeutic products and the fact that the average clinician is knowledgeable primarily with respect to the 80 to 100 drugs that he commonly uses, having access to a robust drug information source is essential.

In the case in which it is determined that the drug is responsible for the adverse event, one moves to the next step, assistance. The treatment of ADRs is primarily supportive and symptomatic, with certain exceptions. In the case of very severe acute reactions such as anaphylaxis, acute management focusing on airway, breathing, and circulation is critical. When the ADR is a serious immune-mediated event, as in the case of Stevens-Johnson Syndrome, there is increasing evidence⁴⁵ that immune modulation may reduce the severity and duration of symptoms. In this case, consultation with an expert in this area is important. For most ADRs, management of symptoms is appropriate while the reaction resolves. One issue that is not often considered is the management of the initial condition being treated. If the condition has been resolved, then discontinuing the offending medication is a justified and prudent decision. In the case in which the initial condition requires ongoing management, then the decision is more problematic. When side effects that will likely to resolve over time occur during therapy for serious conditions, an option is to continue treatment (after discussion with the patient and family); this has been done very successfully in the context of HAART therapy for HIV infection.⁴⁶ In the case of children, one of the most common examples is the management of tremor when beginning therapy with inhaled albuterol.⁴⁷

The final step, aftermath, is unfortunately often not considered. Part of aftercare following an ADR is the communication with the patient and family as to what occurred, what the role of drug therapy was in the event, and what drug(s) the patient should avoid in the future.¹⁶

This also must be communicated clearly to the clinicians in the circle of care, as many of the children at highest risk for ADRs are not only receiving many medications but frequently are cared for by many clinicians. In addition, an unappreciated impact may involve compliance. It is reasonable to assume that when a family or patient is asked to take another medication in the context of having sustained an adverse event to another medication, compliance, which in the setting of chronic disease is rarely optimal, can be markedly affected.¹⁶

Pediatric Pharmacy and Drug Safety

Currently there are more than 3600 therapeutic products available for the treatment of children in the United States and Canada, with approximately 20 to 30 new drugs entering the market every year.^{1,48} Thus, a clinician entering practice is likely, over the course of a 30-year career, to need to consider how to evaluate, incorporate, or not use 600 to 900 new therapeutic entities. Although emerging regulatory changes mandating pediatric content are likely to enhance the labeling of drugs for children, strategies for niche approvals as well as the concurrent use of new drugs and older agents means the problem of off-label use will not disappear any time soon.⁴⁹ This is a major challenge.

An additional emerging issue is the nature of the new therapeutic entities. The “Therapeutic Revolution” that began with the observation of the antimicrobial activity of Prontosil has largely been driven by the discovery of small molecules. Over the past decade, and notably over the past 5 years, this has changed dramatically, such that in many jurisdictions up to half of new drug approvals are biological, including proteins, antibodies, factors, and other novel large molecules.^{49,50} While we have a number of tools and approaches for studying small molecule pharmacology in children, the tool kit is less robust for biologics.

In this context, the role of pediatric pharmacy becomes a more and more important part of a robust patient safety strategy. The first venue in which this applies is the clinical arena. As outlined above, a key area in which pediatric pharmacists have a major role in terms of gathering key information is the specific event in question, which is then informed by the latest drug information as to the therapeutic agent in question. For this very reason, clinical pharmacists are an essential part of pediatric care teams, notably in areas such as Neonatal Intensive Care Units and on teams managing children with complex chronic disease. As well, legislative changes that permit prescribing by pharmacists allow increased involvement in—and mandating increased responsibility for—selection of therapy for children. Current training programs in pediatric pharmacy are very well designed to produce the next generation of practitioners as active members of patient care teams.

Education is another area in which pediatric phar-

macy can play a crucial role in teaching skills germane to patient and drug safety. As medical schools have evolved, a common theme across North America has been the need for more focused teaching in therapeutics. This is even more so the case with regard to pediatric residencies. In these cases, and notably for residency training, the pediatric pharmacist can fill a valuable role as an educator and patient advocate.

The final area in which pediatric pharmacy is important is research. Over the past 3 decades, many of the key safety discoveries in drug safety for children have included pediatric pharmacists on the research teams working on these questions, in many cases being driven by pediatric pharmacists. Our expanding knowledge of human biology has been matched by a new set of tools; a challenge, as noted above, is modifying and applying these tools to allow for study of therapeutic questions in children.

In *Hamlet*, Shakespeare characterized the future as “the Undiscovered Country.” As we move to chart our way forward in pediatric therapeutics, pediatric pharmacists will need to take a leading role in ensuring safe as well as effective treatment for children.

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