ELSEVIER

Pediatric Drug Allergy

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The problem of adverse reactions to drugs in the pediatric population is an important one that has only recently received appropriate attention. Much of this relates to the special process of drug evaluation for the pediatric population, which was very limited until the last decade or so. It is very similar until recently to the assessment and predictability of adverse drug reactions in women. Most of the major references focusing on this have occurred since the mid-1970s. This is a particularly key area because of the very common problem of morbilliform eruptions in the pediatric population, which can relate to a number of possibilities, including drug allergy, in the differential diagnosis. These morbilliform eruptions can represent childhood exanthems from the various viruses (see Table 1 and 2). It is imperative in each patient presenting with a morbilliform eruption that the full differential be entertained, so as to not miss potential serious sequelae. Our expanding knowledge of adverse drug reactions in the pediatric population allows, in this review, to cover 1) incidence, 2) the evolving understanding of mechanisms, 3) the differential diagnosis, and 4) newer approaches to therapy.

Incidence—Children, Sex, Adults

Evolving data on the difference in age as well as sex, incidence is presented in a recent article on cutaneous rates of drugs in the *Archives of Dermatology*.[1] From this, the latest article is a study of overall reactions to drugs, with much of the data coming from the Boston Collaborative Drug Study. In adults, it is reported that women have a 35% higher reaction than men. In contrast, reports that the Comprehensive Hospital Drug monitoring (CHDM) data from Switzerland reported by Sonntag et al[2] show the difference ratio of 0.9 in boys and girls younger than 10, 1.05 in those younger than 14, and 1.63 in those 18 years of age or older. Some of these data, we believe, relate to greater drug consumption by women and a greater usage among the elderly, which creates the significant difference in data from the Boston Collaborative Study. The data by Ibia et al[3] note that 92% and 82% of rashes occurred in boys and girls 6 years and younger, respectively. Most of the studies indexed in the survey show an increasing female/male ratio with age. Therefore, with progression to adulthood, this susceptibility begins initially with a male predominance in studies in Holland,[4] Switzerland,[2] United States,[1] and others and ultimately, with achieving adulthood, where the female preponderance in drug reactions occurs. (Female/male ratio is 1.58 in Italian regions.[5]) Studies such as these meta-analyses have greatly added to our overview of incidence in such drug reactions.

Mechanisms/Pathophysiology/Definitions

Traditionally, classifications have included several subsets. Even the definition of drug-induced disease has several definitions,[6] beginning with the World Health Organization (WHO), one of 30 years' standing:

> "A response to a drug that is noxious and unintended, and occurs at doses normally used in man, with a prophylaxis diagnosis or therapy of disease, or for modification of physiological function."[6]

Lawrence et al[7] modified this some, excluding some of the minor minimally troublesome reactions:

> "A harmful or significantly unpleasant effect caused by a drug at doses intended for a therapeutic effect (or prophylaxis or diagnosis), which warrants reduction of dose or withdrawal of the drug, and/or foretells hazard from future administration."[7]

Edwards and Aronson, in their recent review,[8] point out a new twist on the concern over adverse reactions or drug-induced disease. This is pertinent to the burgeoning field of alternative medicine and herbal medicine, wherein complex compounds "i.e., natural products," may and often do contain contaminants that can be potentially harmful via toxicity or drug interaction. Their new definition is:

> "An appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product which predicts hazard from future administration, and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product."[8]

Lately, the American Academy of Dermatology weighs in with the definition "an adverse cutaneous reaction caused by a drug is any indescribable change in the

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Table 1. Classic exanthems

Rubeola
Rubella
Scarlatina
DUKES—Rubeola-scarlatina, pseudoscarlatina
Fifth disease—erythema infectiosum
Sixth disease—exanthema subitum; roseola

structure or functions of the skin, its appendages or mucous membranes".[9]

Further, the guideline committee notes; "Adverse reactions may result from overdose, accumulation, pharmacologic side effect, drug-drug interactions, idiosyncrasy, microbiologic imbalance, exacerbation of existing latent or overt disease, Jarisch-Herxheimer reaction, hypersensitivity, autoimmune-like reaction, teratogenic effect, interaction of the drug and sunlight or other light sources (i.e., artifical tanning devices), or other unknown mechanisms."[9]

While this may seem the extreme of quibbling, it is becoming of increasing significance because of the burgeoning practice of polypharmacy and the serious potential for drug interactions, more so in adults than in children. This exercise points out the difficulty in defining the problem and recent changes in perspective.

The old categories of drug-induced disease or unwanted drug reactions included physiological and also metabolic or toxic side effects; drug interaction; allergic or "pseudo-allergic," including hypersensitivity; and the catch-all idiosyncratic. Rawlins and Thompson[10] in the last decade simplified this some into two categories, type A reactions, which are predictable and related to pharmacological actions of the drug (including toxicity, side effects, secondary effects—i.e., altered physiological function due to alteration in the body's ecology and drug interaction, and type B. The other category, type B, includes drug intolerance, immunological reactions, and pseudo-allergic reactions.[10] To add to the confusion, Edwards and Aronson[8] proposed six types, including their mnemonics:

- augmented (dose related)
- bizarre (non-dose related)
- chronic (dose and time related)
- delayed (time related)
- end-of-use withdrawal
- failure—failure of therapy

Table 2. Diagnosis of morbilliform eruptions

Viral (see Table 1) exanthems
Drug (see Table 5)
Strep scarlatina
Staph scarlatina
Toxic shock syndrome
Kawasaki disease

Table 3. Traditional classification of drug eruption

I	Allergic
II	Physiological/metabolic
III	Toxic
IV	Overdosage (relative, related to drug interaction)
	Secondary

This, however, may be a useful classification because it does reinforce remembering all types of reactions, which is essential in the predictability of subsequent patient drug exposure, as well as prognosis and therapeutic import.

Perhaps the greatest utility of separating type A and type B has to do with prognostication and future potential for reactions, as well as reactions across similar classes of drugs. Of primary significance to the clinician are the type B hypersensitivity reactions because of immune amplification by the body, which may, with subsequent antigenic exposure, cause ever more serious reactions with smaller antigen presentation. Most of the other drug reactions are very much dose related, and this is of significance to the treating physician. The pathomechanisms of certain drugs as representative of these different mechanisms are listed in Table 3.

Immunological Reactions

The type B allergic reaction primarily has mechanisms currently numbered at four, but growing with our understanding of the pathophysiology. Traditionally, we have used the Coombs and Gel system of immunological reactions to classify. These include the usual type I reaction, which is of greatest import because of its potential for anaphylaxis, and common presentation of local or widespread urticaria. The major significance of these reactions is the biological amplification, so that subsequent exposure to the given drug, even in trace amounts, can cause reactions ranging from urticaria to life-threatening anaphylaxis. The mechanisms here center around certain predisposing phenotypes, including the patients in the TH-2 paradigm. TH-2 paradigm patients are those with common skin diseases, such as atopic dermatitis, that have the TH-2 predilection toward overproduction of antibodies, especially those in the immunoglobulin (Ig)E category. Such patients are at greater risk for IgE-induced anaphylactic drug reactions.

The reactions, including the bullous eruptions, toxic epidermal necrolysis, erythema multiforme major (Stevens-Johnson syndrome), may be a function of the type II, or cytotoxic, reaction. Additionally, many cytopenic reactions occur in children, from this type of reaction, including thrombocytopenia and penic states related to other cells of the blood.

The most common form of drug eruption is the type III, or immune complex–related reaction, in regard to

Table 4. Antibiotics and rashes (Ibia et al[3])

Cefachlor	12.3%
Penicillin	7.4%
Sulfonamides	8.5%
Other cepholosporins	2.6%
Overall	7.3% incidence

cutaneous signs and symptoms. The problem with immune complexes and subsequent diseases has been studied for >60 years, and the initial understanding of problems with rate of antibody production, antigen-antibody ratios, the zone of equivalence, etc., all have been worked out in animal models and have greatly enhanced our understanding of the situation in humans. All that remains is development of better techniques to assess the offending antibodies and, more importantly, the offending antigen to confirm unequivocally which drug is the cause for such urticarial and other vasculitic type reactions. This is a very significant category in pediatric patients because of the differential from childhood exanthems and is a major factor in pediatric dermatology (Table 4). This is especially true in the use of penicillins and amino penicillins for childhood infections (Table 5).[2,11] The fourth immunological reaction in the Coombs and Gel system is contact dermatitis, or type IV cell mediated–immune reaction, and under these circumstances, certain drugs have been demonstrated to cause both humorally associated as well as T-cell–mediated reactions. Our understanding of these has changed a great deal, with the increased knowledge of the important role of T cells (helper and suppressor) that effect the B-cell side of the equation.

Nonimmunologic Reaction

Toxicity

No overview is complete without some reference to another aspect of drug reactions; that of toxicity. Several mechanisms apply here: the direct effect of oxidizing drugs on the hematopoietic mass, cell-cell toxicity, and drug-and heavy metal–induced hyperpigmentation are other good examples. Toxicity can also be relative, in that normal dosages of drugs given in combination with other drugs that compete for metabolism or carrier proteins can result in elevated toxicity when perfectly normal and appropriate dosages are being used. This has become very significant in increased use of chemotherapeutic and cytotoxic agents in pediatric practice. Much of these adverse reactions are anticipated, including the classic alopecia from the various cytotoxic agents, which, in some incidences, can be minimized by cooling of the scalp, etc. Additionally, the use of systemic agents and extravasation of same has been a frequent cause for consultation to dermatology to assess the possibilities of minimizing the tissue loss after extravasation of intravenous agents. Many of these intravenous agents are cytotoxic as the direct action of the drug, but in others, including some of the antibiotics (historically, tetracycline was one), were indirect, where the infusion material was cytotoxic by basis of excipients, additions, or pH that is toxic to the dermis where it infiltrates. This type of reaction is nonimmunologic and is virtually always predictable, well-known, and should in many incidences be preventable.

Although often a "wastebasket" term, the so-called "idiosyncratic reaction" has become an increasingly significant one in the spectrum of drug reactions. The idiosyncratic reaction, by definition, lacks precision and specificity in etiology and development, but with the increasing awareness of these reactions, a clearer picture is evolving of the development and evolution of such. With this new knowledge, better predictability in the future seems certain. Of significance is the role of reactive drug metabolites in these reactions.[12] This partially explains some of the differences within classes of drugs, such as the interesting predominance of cefaclor as a major cause of such reactions to antibiotics in pediatrics. The recent excellent review covering reactions to the antibiotics underscores the significance of these drug, which seem particularly prevalent in the pediatric age group, and is of much less significance in antibiotic drug reactions in adults.[3] Whether this is a function of differences in metabolism of these drugs in the pediatric patient versus adults, related to maturation of such enzyme systems for oxidation-reduction (redox), hydrolysis, and subsequent conjugation that render these inactive compound water soluble for renal excretion, is uncertain. The list of various idiosyncratic reactions does include many antibiotics and antibiotic-like drugs, including the sulfas and sulfones. Also, the anemia with such (oxidizing) drugs in patients with glucose 6-phosphate dehydrogenase deficiency and various hepatic reactions, such as cholestasis and others reactions, still have an unclear biochemical basis.

Interactions

Drug interactions resulting in significant reactions are less common in the pediatric age group simply because polypharmacy is less common. In contrast, the older patients who are taking two to five different medications are exposed to much greater risk of interactions related to such simple mechanisms as competition with the cytochrome P450.3A system in breakdown, which can result in elevated and sometimes toxic levels of certain drugs; in the geriatric population, this becomes a very significant problem (Table 7). Infants and children, as mentioned above, are at much lower risk, but occasionally, reactions can occur. The classic prototype for many years has been theophylline toxicity with the introduction of erythromycin therapy. The newer drug interactions with this drug via the CP450.3A interaction

Table 5. Drug exanthems—etiology

Antibiotics	Penicillin, ampicillin, cephalosporins, erythromycin, sulfonamides
Antiseizure	Phenytoin and derivatives, barbiturates, carbamazepine
Anti-inflammatory	Nonsteroidals, gold phenylbutazone
Antianxiety	Phenothiazine, benzodiazepines

has been a surprise; for many years, erythromycin and other macrolides were considered among the safest of antibiotics. This remains true in monotherapy—often the case in children who are rarely on the polypharmacy that is the rising concern in adults.

Similarly, the use of the tetracycline group of drugs and their ability to be deposited in the developing teeth of the fetus or child under age 7 provide a well-known contraindication for the use of these drugs.

Metabolic

Metabolic actions of drugs include their ability to alter absorption with some notable examples including 1) phenobarbital inhibiting the absorption of griseofulvin and many acidic drugs (coumadin, sulfa). These are metabolically bound to albumin and may compete with each other for binding sites, and in the case of coumadin therapy, this can result in significant toxicity. Similarly, sulfonamides and aspirin can increase methotrexate toxicity in the patients on chemotherapy for malignant disease. The biggest area of metabolic concern has to do with the drug metabolism by the various cytochrome systems and the significant interaction in patients on multiple drugs. This is highlighted in Table 7 and one of the earliest examples was the cardiac toxicity related to astemizole in conjunction with other drugs (macrolide,[5] imidazoles, and others listed on Table 6) in the pediatric patient with seizure disorders; similarly, challenges arise with the use of various agents, including the barbiturates, fentanyl, and their derivatives, with their interactions with the metabolism of griseofulvin, anticoagulants, and some agents used in transplants. The more aggressive and very successful treatment of childhood malignancies and successful transplant therapy

Table 6. Drug interactions

Class	*Example*	*Comments*
Macrolides		
Certain macrolides increase the following drugs due to cytochrome P450 inhibition*		
Bronchodilators	Theophylline	Increased risk of central nervous system toxicity
Anticonvulsants	Carbamazepine	Other anticonvulsants not affected
Signal transduction inhibitors	Cyclosporine, tacrolimus	Increased risk for nephrotoxicity and neurotoxicity
Corticosteroids	Methylprednisolone	Lesser effect on other corticosteroids
Benzodiazepines	Alprazolam, diazepam, midazolam, triazolam	Greater risk of sedation
Increased risk of torsades de pointes with macrolides		
Azole antifungals	Terfenadine, astemizole	Both off the market in U.S.
Prokinetic gastro intestinal agents	Cisapride	Off the market in U.S.
Fluoroquinolones		
Drugs that reduce fluoroquinolone levels		
Antacids	Calcium, aluminum, magnesium	Chelation to divalent and trivalent cations
Salts	Iron and zinc	Chelation
Fluoroquinolones increase levels of the following		
Bronchodilators	Theophylline, aminophylline	Theophylline levels may be tripled
Anticoagulants	Warfarin	Increased pro-time/international normalized ratio
Other fluoroquinolone interactions		
Signal transduction inhibitors	Cyclosporine	May increase creatinine levels in transplant patients
Tetracyclines		
The following may reduce absorption of tetracycline's		
Other cations	Calcium, magnesium, aluminum	Chelation to divalent and trivalent cations
	Iron, zinc, bismuth	Chelation
Tetracyclines may increase levels of the following		
Psychotropic agents	Lithium	Monitor carefully
Anticoagulants	Warfarin	Likely due to changes in gut flora
Other interactions		
Insulin		Tetracycline may reduce insulin requirements
Penicillins		May interfere with bactericidal activity of penicillins

** Risk for interaction greatest with erythromycin, moderate with clarithromycin, and negligible with azithromycin and dirithromycin.*
Reference: Wolverton, Stephen E. Comprehensive Dermatologic Drug Therapy, W.B. Saunders Company, Philadelphia, 2001, pp 37, 40, 43.

Table 7. Antihistamine R prescription drugs

	Dose	*Special Indications*
Older/Sedating Antihistamines		
Cyproheptadine (Periactin) 4-mg tabs	2–6 years 0.25 mg/kg/d 2mg BID-TID Do not exceed 12 mg 7–14 years 4 mg BID-TID Do not exceed 16 mg Adults 4–20 mg q day Do not exceed 0.5 mg/kg/d	Allergic rhinitis, cold urticaria, dermatographism, urticaria, angioedema
Hydroxyzine hydrochloride (Atarax) 10-, 25-, 50-, 100-mg tabs Syrup: 10 mg/5 cc	<6 years 50 mg q day divided doses <6 Adults 50–100 mg q day divided Adults 25 TID-QID	Pruritus due to allergic conditions and histamine—medicated pruritis
Newer/Sedating Antihistamines		
Loratadine (Claritin) 10-mg tabs, Syrup 1 mg/ml, 10 mg Reditabs	6–11 years 10 mg q day (2 tsp) >12 years: 10 mg	Seasonal allergic rhinitis and chronic idiopathic urticaria in patients > 6 years mg q day (2 tsp)
Cetirizine (Zyrtec) 5-mg tab, 10-mg tab Syrup: 1 mg/ml	2–5 years: 2.5 mg (1/2 tsp) q day Maximum 5 mg q day 6–11 years 5 or 10 mg q day >12 years: 5 or 10 mg q day	Allergic rhinitis, chronic urticaria
Fexofenadine (Allergra) HCL, 60-mg capsules, 30-mg tablets, 60-mg tablets, 180-mg tablets	6–11 years 30 mg BID >12 years 60 mg BID	Seasonal allergic rhinitis, chronic idiopathic urticaria.

** Physicians' Desk Reference, 55 edition, © 2001 by Medical Economics Company, Montvale, NJ.*

have broadened the menu of agents in this group most capable of both metabolic interactions altering drug toxicity as well as cumulative toxicity. Foremost are the multiple drugs used either in therapeutic immunosuppression, cytotoxic therapy, or transplant therapy.

Lastly, our increasing understanding of some of the other cytokines and the development of new agents that may affect the cytokine release or cytokine effect are broadening our understanding here, also. Some of the best examples include the interleukins—IL-1, IL-2, etc., and most importantly, tumor necrosis factor (TNF). TNF inhibitors are becoming available for clinical use, and as a result, the role of TNF in certain drug eruptions should be much clearer in the near future. It is entirely possible that some drugs may directly stimulate TNF release, and this is thought to be a major factor in some of the noncutaneous adverse drug reactions, including drug fever.

Treatment of Drug Eruptions in Children

Treatment of pediatric drug eruptions is in some ways more complicated than the considerations for adults. In the first instance, the biopsy to determine etiology is usually more of a challenge in young patients whose cooperation is less certain. However, in many adults and elderly patients, the problem of polypharmacy becomes a serious factor in both determination of cause and selection of appropriate treatment. While the pediatric patient may have a simpler drug regimen, differences in body size and surface area make it more of a challenge to determine the appropriate drug, dose, and dosing of it.

Step I

After determination of the drug, within a reasonable certainty, and discontinuation, careful awareness of drug half-life is important to determine the nature of therapy and the aggressiveness of it. It is true that with many antibiotics, the cutaneous reaction worsens for the first few days after discontinuance. This is a function of increasing antibody production as well as increasing avidity and affinity of the antibodies outstripping the slow and steady decrease of the drug as an antigen. Because of this, early on the reaction may get

significantly worse, as the enhanced binding results in immune complexes that enlarge and multiply, significantly worsening the patient's cutaneous symptoms. This frequently raisies the question as to the correct identity of the offending drug. When there is a question of type I or type III reactions, it may be important to use high-dose steroids to decrease the patient's reactivity to the antigen and diminish the reactions to the large immune complex lattices that create problems in the cutaneous vasculature and the subsequent symptoms of vasculitis and urticaria. The worst-case scenario includes anaphylaxis and anaphylactoid reactions.

Step II—General Therapy

In the case of type I reactions, the specter of upper-airway obstruction also mandates the use of epinephrine and other beta-agonists, as well as steroids when the urticarial vasculitis or urticarial reaction is at its peak to forestall major airway problems. Less severe reactions may be very successfully treated with a low tapering dose of steroids and appropriate use of antihistamines, both of the sedating and nonsedating type, which is determined according to the severity of the reaction and the physician's comfort with any given class of antihistamines and availability of the drug for pediatric indices. One cannot stress enough the importance of adequate dosing, especially of the antihistamines, where inadequate drug blood levels often are the cause of treatment failure. One should always choose and prescribe the antihistamine of the physician's choice in adequate dosage to achieve tissue effect. Some examples of the most common antihistamines for maculopapular, pruritic, and urticarial reactions are seen on the accompanying table (Table 7). It is important to recognize that for the pediatric patient, there is available in the United States a number of antihistamines without prescription that are effective, but effectiveness mandates appropriate dosing related to body mass/surface area/weight, which is usually higher dosing than that recommended for over-the-counter (OTC). Often, the family will bring the patient in, having already used Benadryl, Chlor-Trimeton, or Dimetapp, without success (which is available OTC at a low and safe dosage schedule), but when dosage is pushed to appropriate levels per body mass/surface area, they can be quite effective. The prescription agents Claritin®, Allegra®, Zyrtec®, Atarax®, and Periactin® (see Table 6) all are available for pediatric dosing in one form or another. In the case of urticarial drug reactions and those with potential concern for airway involvement, the use of epinephrine may be an essential safeguard. This can be prescribed with the use of the self-administrated Epi-pen® device, so that those patients (both the patient and the family) who manifest IgE hypersensitivity should be aware of and comfortable with the use of such an emergency instrument, for it may be life-saving. The essence of therapy is discovery of cause, elimination of the cause, and treatment of the symptoms. Antihistamines are the primary modality, but should those fail, steroids are often the next step. A short burst of steroids starting at 1 mg/kg prednisone or equivalent tapering over a 2-week course is usually sufficient to control symptoms. This is usually sufficient for all but the most long-acting drugs that have significant tissue distribution/storage and subsequently long half-lives.

Table 8. Drugs reviewed by at least 1000 patients with no allergic cutaneous reactions—likely to be used in Pediatrics—Boston Collaborative Drug Surveillance Program

Milk of magnesia
Acetaminophen
Meperidine
Maalox
Multivitamins
Aspirin
Diphenhydramine
Ferrous sulfate
Regular insulin
Phosphate enema
Vitamin B complex
Magnesium citrate
Folic acid
Lidocaine
Prednisone

While it is not the usual approach in the United States in Europe and other parts of the world, challenge to the suspect drug has and can be done to confirm hypersensitivity. This has certain utility, in allowing and assuring the avoidance of certain drug exposure in the future.

In patients deemed prone to allergic reactions, an awareness of relatively safe medications (see Table 8) is an equally important therapeutic choice—always try to avoid the common drugs causing allergy when possible.

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Coins from the United States, England and Spanish-Mexico circulated freely in Canada prior to 1858. It wasn't until 1858 that Britain minted coins for Canada at the Royal Mint in London. In 1908 the first Canadian mint was established in Ottawa. Denominations 10 cents and greater were minted from silver. Various amounts of copper have been added to the silver alloy throughout the years. With the increasing price of silver in 1967–8, the Canadians reluctantly switched from 50% silver and 50% copper to 100% nickel for the dime, quarter, half and dollar coins. The last year for silver in dimes and quarters was 1968, for half dollars and dollars it was 1967. On the left is a 50% silver quarter, on the right a 100% nickel quarter dollar coin.

From the collection of Raymond T. Kuwahara, MD, Memphis, TN.

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