Adverse Drug Reactions:

When the Solution Becomes the Problem

By Michael Rieder, MD, PhD, FRCPC, FAAP, FRCP(Glasg)

In this article:

1. How are adverse drug reactions classified?
2. What are the risk factors?
3. What are the treatment options?
4. When should the patient be referred?

Drug therapy is one of the cornerstones of modern medicine. Appropriate use of medication provides physicians with the ability to cure many infectious diseases and to control many other diseases.[1] Drug therapy, however, does have associated problems, including the escalating cost of drugs. Another major problem, and one that confronts primary care physicians on a daily basis, is the risk of adverse drug reactions.

Adverse drug reactions (ADRs) are both common and important. It is estimated that 5% of all patients suffer an ADR, and that ADRs account for 5% to 10% of all hospital admissions.[2] ADRs have been named as one of the top six causes of death in Canada and the United States, and the economic cost of ADRs runs into the billions.[2,3]

Table 1

Classification of Adverse Drug Reactions

Predictable
Side effects (usually minor and self-limited events)
Secondary effects (predictable but not inevitable events, *i.e.,* pseudomembranous colitis after lincosamide therapy)
Interactions (alterations in drug effect produced by another drug, disease or food)
Toxicity (effects of drugs in supratherapeutic concentrations)
Unpredictable
Intolerance (disabling or very severe side effects)
Allergic or Pseudoallergic
Idiosyncratic (unanticipated and often severe effects, often in vulnerable sub-sets of patients)

Adapted from Patterson R, DeSwarte RD, Greenberger PA, et al. Drug allergy and protocols for management of drug allergies. Allergy Proc. 1994 Sep-Oct;15(5):239-64.

Treating Adverse Drug Reactions

Table 2

Risk Factors for Adverse Drug Reactions

Previous Personal History of an ADR
Polypharmacy
Extremes of Age
Impairment in Hepatic or Renal (Organ of Elimination) Function
Female Gender

ADRs are classified as predictable or unpredictable[4] (Table 1). Predictable ADRs can be anticipated based on the drug's pharmacology (*i.e.*, drug interactions). Unpredictable ADRs cannot be anticipated based on the drug's pharmacology, (*i.e.,* drug allergy). Of the ADRs most often associated with serious morbidity or mortality, the largest contribution are from unpredictable ADRs, primarily allergic/pseudoallergic ADRs and idiosyncratic ADRs.[5,6]

Is it an ADR?

The possibility of an ADR should be part of the differential diagnosis of any untoward event in a patient on medication. It is important to recognize that there is an inherent bias on the part of the two key players in the therapeutic relationship; when bad things happen to a patient on treatment, the physician most commonly blames the disease, and the patient most commonly blames the drug.

There are a few clues as to whether or not an untoward event is an ADR, including the evaluation of known risk factors (Table 2). The key elements in the evaluation of a possible ADR are a careful history and physical examination.[7] The history should focus on what medication(s) was/were taken, when symptoms developed and what else was going on in the patient's life.

Timing is important; the majority of serious ADRs develop within the first several days or weeks of therapy. With some important exceptions, such as cardiomyopathy associated with chemotherapy, the majority of ADRs occur within the first six weeks to six months of therapy. The nature of the symptoms is also very important, notably as verified by the physical examination. Urticarial rashes are more likely to be due to an ADR than is a polymorphous maculopapular rash. This is especially true in children, in whom exanthems are a common manifestation of viral infection.

Drug interactions are common and become more common the more drugs the patient takes.[8] Drugs can induce the metabolism of other drugs and thus reduce their effects, or inhibit the metabolism of other drugs and thus increase their effects and toxicity.[9] Drugs that induce or inhibit CYP3A4, the most common

Dr. Michael Rieder is a paediatric clinical pharmacologist and head of the clinical pharmacology division, Children's Hospital of Western Ontario and the University of Western Ontario, London, ON.

metabolizing isozyme of cytochrome P450, are listed in Table 3. Not all inducers or inhibitors are drugs; St. John's Wort is recognized as an inducer of CYP3A4, while grapefruit juice is a potent inhibitor of CYP3A4.

The patient's overall health should be evaluated as part of the evaluation of a possible ADR. This will be an important determinant of planning for both management and followup.

Table 3

Common Inducers and Inhibitors of Cytochrome P450 3A4

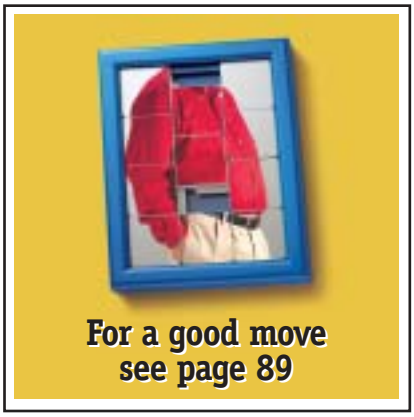
Inducers	Inhibitors	Protease Inhibitors
Carbamazepine	Clarithromycin	Amprenavir
Phenobarbital	Erythromycin	Indinavir
Phenytoin	Cyclosporine	Nelfinavir
Rifampin	Diltiazem	Ritonavir
Dexamethasone	Ketoconazole	Saquinavir
	Itraconazole	
	Nefazodone	

How can I confirm an ADR?

There are very few confirmatory tests for ADRs; as noted above, the major assessment instrument for ADRs is a skilled and careful clinician.[10] Skin testing is available for confirmation of IgE-mediated ADRs to penicillins and local anesthetics, but it should be emphasized that these tests are very specific and are not predictive of ADRs mediated by other mechanisms (*i.e.*, serum sickness-like reactions). Oral challenge is a "gold standard" to determine drug safety, but should only be conducted under controlled circumstances by experts in the evaluation and acute management of ADRs.[11]

How are ADRs treated?

Therapy for ADRs is almost exclusively symptomatic, with several important exceptions. In the case of drug allergy, notably urticarial and anaphylactic reactions, immediate attention to airway, breathing and circulation, and the prompt use of oxygen, bronchodilators, antihistamines and adrenaline are key to avoiding morbidity and mortality.



Treating Adverse Drug Reactions

An often overlooked aspect of therapy is the treatment of the underlying condition. The clinician must determine if the therapeutic goal for which treatment had originally been prescribed has been reached. If the therapeutic goal has been achieved, then it may be reasonable to stop therapy and not have to worry about selecting an alternate treatment plan. On the other hand, if the therapeutic goal has not been achieved, then it is important to undertake the often difficult task of determining which alternate therapy to pursue. It is often helpful in these circumstances to seek consultation from a specialist.

When should I consider referral?

The decision to refer a patient for specialty evaluation and care is largely dependent on the nature and severity of the ADR and on the patient's general health. Patients with severe or life-threatening ADRs, such as penicillin-mediated anaphylaxis, should be evaluated by the appropriate specialist, usually an allergist. In the case of patients with severe ADRs, notably if they continue to evolve despite cessation of the suspected offending agent, consultation with a specialist well-versed in the evaluation and management of ADRs should be sought in a timely fashion.

In addition to specialty consultation, it may be important to notify the Adverse Drug Reaction Program at Health Canada, particularly for severe ADRs and especially for drugs that have been released recently. Although Canada and the rest of the developed world have a careful drug approval process, severe drug hypersensitivity ADRs can occur among susceptible sub-sets of patients who may not have been identified in pre-marketing studies. The vast majority of serious drug hypersensitivities have been identified after the drugs have been marketed and as a result of the clinical acumen of careful clinicians.

What followup should be done?

As in the case of specialty referral, the intensity and degree of followup is largely dependent on the severity of the ADR and the patient's overall health. It is critical that the patient and the patient's family understand what happened, what drug was believed to have caused the ADR and what drugs should be avoided in the future. The patient should also understand whether the original therapeutic goal had been achieved and, if not, how it will be.

Treating Adverse Drug Reactions

The patient should also be advised if further specialty referral is needed and why it is needed. The clinician should appreciate the fact that having had an ADR is likely to impact, at least over the short-term, the patient-physician relationship and that treating the ADR as a separate clinical diagnosis, with a clear plan and with an appreciation for the patient's understandable concerns about future therapy, is the best path back to a solid patient-physician relationship. CME

References

1. Weinshilboum RM: The therapeutic revolution. Clin Pharmacol Ther 1987; 42(5):481-4.
2. Lazarou J, Pomeranz BH, Corey PN: Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279(15):1200-5.
3. White TJ, Arakelian A, Rho JP: Counting the costs of drug-related adverse events. Pharmacoeconomics 1999; 15(5):445-58.
4 Patterson R, DeSwarte RD, Greenberger PA, et al: Drug allergy and protocols for management of drug allergies. Allergy Proc 1994; 15(5):239-64.
5. Naisbitt DJ, Gordon SF, Pirmohamed M, et al: Immunological principles of adverse drug reactions: the initiation and propagation of immune responses elicited by drug treatment. Drug Saf 2000; 23(6):483-507.
6. Rieder MJ: Hypersensitivity adverse drug reactions in children: pathophysiology and therapeutic implications. Curr Ther Res 2001; 62(12):913-29.
7. Rieder MJ, Matsui D: Adverse Drug Reactions in Paediatrics: A Rational Approach". In:Koren G, Diav-Citrin O (eds.): *Bailliere's Clinical Paediatrics, Pharmacology - Towards evidence based drug therapy.* Vol. 6, Number 3. Bailliere Tindall, London, **(Query: Year of publication?)** pp. 505-519
8. Dresser GK, Spence JD, Bailey DG: Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 2000; 38: 41-57.
9. Levy M: Role of viral infections in the induction of adverse drug reactions. Drug Saf 1997; 16(1):1-8.
10. Rieder MJ: *In vivo* and *in vitro* testing for adverse drug reactions. In: Koren G, Bailey B (eds.): *The Pediatric Clinics of North America: New Frontiers in Pediatric Drug Therapy.* Vol. 44, No. 1. WB Saunders, Philadelphia, 1997, pp. 93-111.
11. Matsui D, McLauchlin M, Rieder MJ: Predictive value of oral sulfonamide challenge for adverse reactions. Ped Infect Dis J 1997; 16(11):1084-5.