



Recognizing and preventing adverse drug reactions in children

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Adverse drug reaction (ADRs) – Canada's other drug problem

ADRs rank as one of the top ten leading causes of death and illness in the developed world.¹ The direct medical costs of ADRs are US\$30–130 billion annually in the United States,¹⁻³ claiming 100,000 to 218,000 lives annually.^{2,4} These estimates are even more meaningful when compared with other high-cost diseases like diabetes (\$45 billion),⁵ obesity (\$70 billion),⁶ and cardiovascular diseases (\$199 billion).⁷

Of particular concern is the alarming lack of understanding of ADRs in children. While children are known to be at greater risk than adults, there is a remarkable lack of understanding of causation, and therefore the ability to avoid or prevent these occurrences is limited. Alarming, between 13.7 and 16.6% of paediatric hospitalizations result in ADRs, and 27.9% of these reactions are severe.^{8,9} Each year, approximately 26,500 American children die from ADRs (to age 18 years).¹

Health Canada's records show that health-care providers and pharmaceutical manufacturers reported 1,193 ADRs in children between 1998 and 2002. However, this voluntary reporting system unquestionably reflects only a small proportion of significant ADRs. Health-related accreditation bodies estimate that 95% of all ADRs in Canada are not reported.¹⁰ Systematic examination of medical outcomes is clearly impossible if only 5% of the actual reactions are ever reported.

More than 75% of pharmaceuticals licensed in North America have never been tested in paediatric populations and are used without adequate guidelines for safety or efficacy.¹¹ Until recently, it was assumed that children reacted to medications as 'small adults'. Clinical practice focused on adjusting dosage to account for smaller body mass, with the assumption that clinical effects would be equivalent to those observed in adults.

It is now understood that a host of biological, developmental and behavioural factors impact the safety and effectiveness of pharmaceuticals when used in paediatric

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patients. Anatomic differences in body proportions and age-related differences and body composition distinguish newborns, infants and children from adults. Furthermore, the biological cadence in the developing human is characterized by more rapid pulse and respiratory rates and markedly increased nutritional requirements that are necessary to support a rapid rate of brain and somatic growth.

In addition, children often cannot verbally express their own drug therapy experiences. As a result, newborns, infants and children who require medication for acute, chronic and life saving treatment are at risk of a range of ADRs ranging from ineffective treatment and minor ADRs through severe morbidity and death.^{11,12} It is for these reasons that children worldwide are described as “therapeutic orphans” and are placed at an increased risk of therapeutic failure, while ADRs continue to cause unnecessary disability and death.

What is the definition of an ADR?

The definition of ADR as set out in the Canadian Food and Drug Act and Regulations is “a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of a physiologic function.”

The CPSP ADR study focuses on serious and life-threatening ADR defined as “a noxious and unintended severe response to a drug which occurs at any dose and results in emergency observation, hospitalization, persistent or significant disability, or death.”

What are the mechanisms by which ADRs occur?¹³

ADRs can be classified as either “pharmacological” reactions representing an augmentation of the known pharmacological actions of the drug or “idiosyncratic” reactions that are not predictable.

Pharmacological reactions are most common, usually dose-related and are due to the primary or secondary pharmacological characteristics of the drug. Factors that predispose to these ADRs include dose, pharmaceutical variation in drug formulation, pharmacokinetic or pharmacodynamic abnormalities, and drug-drug interactions. Pharmacological ADRs occur when drug concentration in plasma or tissue exceeds the “therapeutic window” or when there is increased sensitivity to the drug (even in concentrations considered normal for the general population).

Idiosyncratic ADRs are less common, often serious, not dose dependent and show no simple relationship between the dose and the occurrence of toxicity or the severity of the reaction. The toxic reactions may affect many organ systems either in isolation or combination. The mechanism of these is not clear but is thought to include receptor abnormality, abnormality of a biological system that is unmasked by the drug, immunological response, drug-drug interactions, or be multifactorial.



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What is the role of pharmacogenetics in ADRs?

Although many non-genetic factors influence the effect of medications (i.e., age, organ function, and drug interactions), genetic factors are important contributors to the incidence and severity of ADRs.^{12,14-21} In fact, genetic factors contribute to an estimated 50% of ADRs²² and account for 20-95% of drug response variability.²³

The knowledge that specific gene mutations can cause ADRs is not new. Forty years ago it was known that impaired hydrolysis of the muscle relaxant succinylcholine by butyrylcholinesterase was inherited. What is relatively new is the ability now to interrogate on a genome wide scale the genetic determinants of ADRs.

More than half of the drugs causing ADRs are metabolized by at least one enzyme with a variant allele known to cause poor metabolism (i.e., cytochrome P450 enzymes).²⁴ In addition, there are now numerous examples of other classes of genes that have variants that occur with moderate-to-high frequency and are believed to influence the response to drugs, such as drug transporters (i.e., ATP-binding cassette family of proteins) or drug targets (i.e., α_2 -adrenoreceptor and arachidonate 5-lipoxygenase) and their associated pathways. There are many additional precedents for genetic determinant of ADRs²⁵ and these pharmacogenetic mutations can be single nucleotide polymorphisms, insertions and deletions, variable numbers of tandem repeats, gene deletions and duplications. Recurring themes include common variants or a larger number of rare variant alleles which often show striking differences in ethnic groups. These findings are important not only because of the specific variants that have been identified, but also because they suggest that it will be possible to find many of the variants that we do not yet know about. Unlike other factors influencing drug response, inherited determinants remain stable throughout a person's lifetime. As our knowledge of genetic variations involved in the uptake, distribution, metabolism, and action of drugs improves we will be able to select the best drug at the optimal dose for each patient.

Misconceptions about ADR reporting²⁶

- **All serious ADRs are documented by the time a drug is marketed** – Most new drugs have only been tested on a small patient population for a relative short period of time. However, given that many serious ADRs occur at low frequencies, they are often not detected. In the paediatric population this situation is even more acute.
- **It is difficult to determine if a drug is responsible** – Even though it may be impossible to determine definite causality of an ADR, especially in complex situations with multiple disease conditions and drug therapies, the temporal relationship of a reaction with regard to the administration of a new medication



and the biological plausibility may allow the ADR to be classified as possible or likely causative. All potential ADRs should be reported.

- **ADRs should only be reported if absolutely certain** – A reporter of an ADR does not need to be absolutely certain that the suspected drug has caused the reaction. All ADR reports contribute to the awareness of drug safety and should be reported.
- **One reported case can't make a difference** – History shows that regulating authorities often respond to a single clinical report of a serious ADR, leading to further investigation of a drug's safety. Given that pre-marketing trials cannot identify all rare ADRs to a drug, it is very important to report.

Identifying and preventing ADRs – Key points for practitioners

- Take a medication history
- Have a high index of suspicion that an ADR may have occurred if untoward effects are seen with recently initiated or changed drug therapy
- Be aware of the toxic profile of prescribed drugs
- Manifestations of drug toxicity can be variable and affect any organ system
- The potential for ADRs increases with the number of medications prescribed
- ADRs due to drug interactions may be due to drug effects on metabolic pathways, enzyme induction (increased metabolism) or enzyme inhibition (decreased drug clearance).
- ADRs can mimic other diseases

The importance of completely filling in the CPSP ADR report form data fields

The ADR reports received by Health Canada and researchers are often characterized by missing data fields. In a review of the 1193 paediatric ADRs reported to Health Canada between 1998 and 2002; drug dosage form, dose of the drug and frequency of dosage administration were missing in more than 50% of the reports. In the CPSP ADR study we request information on time of the onset of the reaction as well as duration and time of onset of drug therapy. These are important pieces of information to have for causality assessment of the ADR. A complete report of the ADR ensures that valuable information about drug safety is not lost.

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Quiz

1. Which of the following statements is true?

- a) ADRs are one of the top ten leading causes of death and illness in the developed world.
- b) Children are at greater risk for ADRs than adults.
- c) Less than 95% of ADRs are reported.
- d) More than 75% of pharmaceuticals licensed in Canada have been tested in children.
- e) a, b, and c
- f) All of the above

2. Factors that predispose children to ADRs include:

- a) anatomic differences in body proportions
- b) smaller body mass
- c) inability to express their experience
- d) all of the above

3. Idiosyncratic ADRs are:

- a) less common
- b) often serious
- c) dose-dependent
- d) a and b
- e) a, b, and c

4. Genetic factors contribute to an estimated 50% of ADRs and account for 20-95% of drug response variability.

- a) True
- b) False

5. Which of the following statements is false?

- a) All serious ADRs are documented by the time a drug is marketed.
- b) ADRs should only be reported when there is absolute certainty.
- c) One reported case can't make a difference.
- d) None of the above
- e) a, b, and c

6. Without the time of medication administration and the time of onset of ADR symptoms, it is impossible to assess ADR causality.

- a) True
- b) False

7. Factors to consider when identifying and preventing ADRs:

- a) The patient medication history
- b) The toxic profile of prescribed drugs
- c) The possibility of ADRs to mimic other diseases
- d) The potential for ADRs to increase with the number of medications prescribed
- e) All of the above

1-e, 2-d, 3-d, 4-a, 5-e, 6-a, 7-e
Answers: