

PEDIATRIC PHARMACOTHERAPY

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A BASIC GUIDE FOR REPORTING ADVERSE DRUG REACTIONS

Adverse Drug Reactions

- [Why Report ADRs?](#)
- [How to Report ADRs](#)
- [MEDWatch](#)
- [VAERS](#)
- [Literature Cited](#)

Poisoning Prevention

Pharmacology Reviews

- [Caffeine Review](#)
 - [Epoetin](#)
 - [Metoclopramide-Induced Increase in Aldosterone](#)
 - [Lamotrigine](#)
 - [Oral Contraceptives](#)
 - [Parenteral Nutrition](#)
 - [Smoking Cessation](#)
-

A BASIC GUIDE FOR REPORTING ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) encompass any new signs or symptoms other than the desired effect of a drug which occur at therapeutic doses. ADRs may be well known, such as the sedative effects seen in 50% of patients after starting phenobarbital therapy, or less common such as pancreatitis associated with valproic acid. ADRs fall into three basic categories: pharmacologic reactions

which are an extension of the drug's desired effect, hypersensitivity reactions, and idiosyncratic reactions which are unrelated to dose or serum drug concentration (1,2). This latter category may not be an entirely random occurrence. Current research has focused on the potential for a genetic predisposition to these reactions.

The frequency of ADRs has been assessed using both short-term surveillance studies (intensive surveys of small patient populations) and long-term results from ongoing reporting systems. Several surveillance studies have attempted to define the prevalence of ADRs in children. The overall incidence appears to be approximately 3-5% in both inpatient and outpatient settings, similar to that seen in adults (1,3). Approximately 2% of pediatric hospital admissions are the result of ADRs (4,5). The most frequent medications cited include antineoplastics, anticonvulsants, antibiotics, steroids, and theophylline. At UVA, 249 ADRs were reported in the two-year period of 1993 and 1994. Of those reports, 22 (9%) involved children.

As expected of critically ill patients, the incidence of ADRs in NICU patients is much higher, 11 to 30%. Bonati and colleagues (6) found a greater number of ADRs in premature infants when any of the following factors were present: gestational age < 28 weeks, diseases such as RDS, apnea, or NEC, use of mechanical ventilation, use of total parenteral nutrition, and impaired renal or hepatic function.

One of the most difficult aspects of ADR assessment is the determination of causality. Often only a temporal relationship between drug administration and the development of an adverse effect can be established. To help identify the likelihood of an association between drug and effect, the following criteria may be useful. Drug reactions, particularly hypersensitivity, most frequently occur within the first month of treatment. Symptoms usually subside within days of withdrawing the drug (dechallenge). A response which occurs again once the drug is reintroduced (a positive rechallenge) is a strong indicator of a drug-effect relationship. Lastly, an immunologic response may be detectable in some hypersensitivity reactions.² In addition, nomograms have been developed to assist with the evaluation of causality (7,8).

Why Report ADRs?

Although the need to document ADRs may seem obvious to most health care professionals, many fail to participate in a reporting system. Recent events have clearly demonstrated the significance of reports initiated by health care professionals. Temafloxacin was removed from the market after identification of drug-induced hemolytic anemia and renal failure. Restrictions were placed on felbamate following reports of aplastic anemia and hepatotoxicity. Many ADRs only become apparent after a drug is in wide-spread use. The limited number of subjects in pre-approval drug investigations, as well as the use of lower doses and the exclusion of patients most likely to suffer an ADR, such as those with

impaired renal or hepatic function, make it unlikely that all possible ADRs will be revealed before final FDA approval for marketing.

As a result, postmarketing surveillance remains a significant part of ongoing efforts to provide safe and effective therapy for our patients. Under-reporting remains a problem. One potential barrier to reporting has been the time required to complete all the necessary paperwork. The FDA has recently made improvements in their program to reduce this problem and facilitate reporting. The FDA has several options for responding to ADR reports. Manufacturers may be required by the FDA to provide direct notification to health care professionals ("Dear Doctor" letters) or make labeling changes. For severe reactions, the FDA may require removal of the drug from the market. In addition, several steps may be taken to prevent ADRs at the institutional level. Methods reported to reduce the occurrence of ADRs include: improving the documentation of patient allergy/drug reaction histories, educating staff about proper medication administration, improving techniques for patient monitoring, and pursuing further investigation through formal drug utilization evaluations (9,10). Several of these methods have been used at UVa. For example, an increase in reports of red man syndrome following vancomycin administration led to an educational program for nurses about the appropriate rate of vancomycin infusion. A report of arrhythmias in a premature neonate following administration of intravenous potassium chloride led to the creation of new policies and procedures mandating slower potassium infusion rates and the use of flush solutions.

How to Report ADRs

Maintenance of an ongoing documentation program is a standard for JCAHO (9,11). At UVa, the ADR reporting system is a function of the Drug Information Center. Health care professionals at UVa need only to contact a pharmacist or the Drug Information Center to report an ADR (phone 924-8034). Health care professionals may also report ADRs through MIS, using the ADR pathway under the master guide. This pathway is currently being revised to more closely follow FDA reporting requirements. The new system will be available on April 1, 1995. The Drug Information Center automatically receives a copy of these reports and will provide follow-up. All serious ADRs are then reported to the FDA through the MEDWatch system.

MEDWatch

If assistance from a pharmacist is not available, any health care professional may initiate a report via the FDA's MEDWatch system. This program was developed in 1993 to simplify documentation in an effort to increase reporting.¹² The one-page form contains all the instructions needed to report an ADR. The respondent is asked to provide all information pertinent to the reaction. Assessment of the causality is not required. In addition to drug-related events, problems with

medical devices, biologics (except vaccines), and special nutritional products such as enteral nutrition products and infant formulas may be reported through the MEDWatch system.

The MEDWatch form contains spaces for a description of the reaction, lab information, and pertinent medical history. Spaces for two drugs are provided, in the event that the cause of the reaction is not certain or if the reaction is the result of a potential drug interaction. The form also contains a checklist to classify the type of reaction. Although any ADR may be reported, the FDA is primarily interested in serious reactions. The following patient outcomes are considered serious and should be reported if believed to be due to an ADR:

- death
- life-threatening complications
- hospitalization (initial or prolonged)
- disability if significant, persistent, or permanent
- congenital anomalies
- a reaction which requires medical intervention to prevent damage, such as the administration of N-acetylcysteine following acetaminophen overdose

A copy of the report should be forwarded to the Drug Information Center for their records. After completion, the form may be folded, sealed and mailed to the FDA. The form may also be transmitted by facsimile to 1-800-FDA-0178. ADRs may also be transmitted via modem to the FDA at 1-800-FDA-7737. It is suggested that you prepare the form in advance to minimize the time required to be on-line. To receive additional MEDWatch forms, contact the pharmacy or call 1-800-FDA-1088. With the present system, there is no need to make an additional report to the manufacturer.

All information sent to the FDA remains confidential. You will be asked to provide an identifier for the patient, so that you can refer to the patient's records in the future. Do not submit the patient's name or social security number. The name of the reporting health care professional remains confidential as well.

VAERS

Adverse reactions related to vaccine administration may be reported through a joint CDC/FDA program. The Vaccine Adverse Event Reporting System (VAERS) was developed as part of the National Childhood Vaccine Injury Act of 1986 to assess the risk of vaccines in US children.¹³ Unlike the voluntary MEDWatch system, reporting through VAERS is mandatory. Reactions that must be reported include:

- death or any other permanent complication associated with any vaccine
- anaphylaxis or anaphylactic shock within 24 hours of vaccination with DPT, P, DT, Td, MMR, or inactivated poliovirus vaccine
- residual seizure disorders associated with any of the above vaccines

- encephalopathy occurring within 7 days of administration of DTP, P, DT, Td or T toxoids and 15 days of administration of MMR
- shock/collapse or hypotonic-hyporesponsive episodes following DTP or any product containing a component of the DTP vaccine
- paralytic poliomyelitis occurring within 6 months in a patient or contact of a patient who has received oral poliovirus vaccine

In addition, any other significant reaction believed to be related to the administration of a vaccine may be reported. To initiate a VAERS report, call 1-800-822-7967. All primary care and emergency department physicians should receive a copy of the VAERS form annually. As with other adverse reactions, a pharmacist is available to assist with completion of these forms when requested. The CDC will contact the reporting health care professional at 60 days and 1 year after submission of a report for any additional follow-up information. All patient and provider information remains confidential.

Reporting ADRs is vital to improving our knowledge of the therapies we use. Particular importance should be given to reporting ADRs occurring in pediatric subgroups such as neonates and adolescents. These groups are often the last to be included in clinical trials but may be the most likely to be affected by differences in metabolism and hormonal responses to drug therapies.¹⁴ Thorough documentation is essential to protect our patients and allow us to truly assess the benefit-to-risk ratio when considering therapeutic agents.

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Literature Cited

1. Leary PM. Adverse reactions in children: Special considerations in prevention and management. *Drug Safety* 1991;6:171-82.
2. Blaiss MS, deShazo RD. Drug allergy. *Pediatr Clin North Am* 1988;35:1131-47.
3. Kramer MS, Hutchinson TA, Flegel KM et al. Adverse drug reactions in general pediatric outpatients. *J Pediatr* 1985;106:305-10.
4. McKenzie MW, Marchall GL, Netzloff ML et al. Adverse drug reactions leading to hospitalization in children. *J Pediatr* 1976;89:487-90.
5. Mitchell AA, Lacouture PG, Sheehan JE et al. Adverse drug reactions in children leading to hospital admission. *Pediatrics* 1988;82:24-9.
6. Bonati M, Marchetti F, Zullini MT et al. Adverse drug reactions in neonatal intensive care units. *Adverse Drug React Acute Poison Rev* 1990;9:103-18.
7. Kramer MS, Leventhal JM, Hutchinson TA et al. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. *JAMA* 1979;242:623-32.
8. Hutchinson TA, Leventhal JM, Kramer KS et al. An algorithm for the operational assessment of adverse drug reactions. II. Demonstration of reproducibility and validity. *JAMA* 1979;242:633.
9. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm* 1992;49:2229-32.

10. Evans RS, Pestotnik SL, Classen DC et al. Preventing adverse drug events in hospitalized patients. *Ann Pharmacother* 1994;28:523-7.
 11. ASHP guidelines on adverse drug reaction monitoring and reporting. *Am J Health-Syst Pharm* 1995;52:417-9.
 12. Kessler DA. Introducing MEDWatch: A new approach to reporting medication and device adverse effects and product problems. *JAMA* 1993;269:2765-8.
 13. Chen RT, Rastogi SC, Mullen JR et al. The vaccine adverse event reporting system (VAERS). *Vaccine* 1994;12:542-50.
 14. Nightingale SL, Hoffman FA. MEDWatch and adolescence. *J Adoles Health* 1994;15:279-80. Editorial.
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POISON PREVENTION WEEK

March 19-25th is National Poison Prevention Week. The theme of this year's campaign is "Everything at Grandma's Isn't Candy" to highlight the need for poison prevention at all places that children visit. Each year, more than 1 million children are poisoned. The majority of these events occur in children less than 6 years of age (1-3). Approximately 10-15% of poisonings in this population occur at places other than the child's home (4).

This month is an ideal time to remind families of the importance of proper storage of medications and other potentially hazardous materials. Key questions to ask include:

- Are all medications (including vitamins and other over-the-counter products) in containers with child-proof caps?
- Are medications stored in a secure place that a child cannot reach?
- Are all household chemicals (cleaning products, dishwasher detergents, etc.) stored in their original containers? Most products are sold in child-proof containers and contain information on contents and treatment of poisoning.
- Are these products stored in a secure place?
- Check the garage or workshop. Are all hazardous products kept in a secure, locked place?
- Do you know how to contact the poison control center or gain access to emergency medical personnel?

Additional patient/parent information is available through the UVa CMC pharmacy (phone 982-0920) and the Poison Control Center (phone 924-0347).

Literature Cited

1. Litovitz TL, Clark LR, Soloway RA. 1993 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 1994;12:546-84.

2. Lovejoy FH, Robertson WO, Woolf AD. Poison centers, poison prevention, and the pediatrician. *Pediatrics* 1994;94:220-4.
 3. Litovitz T, Manoguerra A. Comparison of pediatric poisoning hazards: An analysis of 3.8 million exposure incidents. *Pediatrics* 1992;89:999-1006.
 4. Polakoff JM, Lacouture PG, Lovejoy FH. The environment away from home as a source of potential poisoning. *Am J Dis Child* 1984;138:1014-7.
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Pharmacology Literature Review

Caffeine Review

Although only a small section is devoted to the treatment of apnea of prematurity, this review provides an excellent source of information on the mechanism of action and adverse effects of caffeine administration. This paper also includes a brief discussion on the proposed mechanisms of caffeine tolerance and adaptation. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995;49(1):37-50.

Epoetin

The use of recombinant erythropoietin in diseases other than renal failure are presented in this extensive review. Applications in surgical cases, anemia associated with chronic disease, sickle cell disease, and anemia of prematurity are discussed. In addition, the pharmacokinetic and pharmacodynamic properties of epoetin are described as well as guidelines for dosing. Markham A, Bryson HM. Epoetin alfa: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in nonrenal applications. *Drugs* 1995;49(2):232-54.

Another epoetin review this month focuses on its use in treating anemia of prematurity. This paper addresses the numerous controversies surrounding this use, including proper patient selection, dosing strategies, and cost-benefit issues. Wandstrat TL, Kaplan B. Use of erythropoietin in premature neonates: controversies and the future. *Ann Pharmacother* 1995;29(2):166-73.

Metoclopramide-Induced Increase in Aldosterone

A case of increased aldosterone serum concentrations in a premature neonate is reported. The patient received metoclopramide therapy (0.5 mg/kg/day) for a

period of approximately 1 month before becoming symptomatic. Excessive weight gain, as well as urinary electrolyte imbalances were noted. The patient recovered within a week of discontinuing therapy. Fanning S et al. Possible metoclopramide-induced increase in serum aldosterone in a premature infant. *Am J Health-Syst Pharm* 1995;52(3):316-7.

Lamotrigine

This review focuses on lamotrigine, a recently marketed anticonvulsant for use in adults with partial seizures. Lamotrigine also appears to be an effective add-on therapy for children with refractory partial seizures. In addition, it has been used to treat children with Lennox-Gastaut syndrome. Dosing and monitoring guidelines are included. Gilman JT. Lamotrigine: An antiepileptic agent for the treatment of partial seizures. *Ann Pharmacother* 1995;29(2):144-51.

Oral Contraceptives

This is a very brief summary of the different formulations available, drug interactions and current recommendations on choice of agents in specific patient groups. A section on adolescents is included, but provides little substantial information. This article is worth reviewing, however, for its useful tables including one providing instructions for when a patient misses a dose. Weisberg E. Prescribing oral contraceptives. *Drugs* 1995;49(2):224-31.

Parenteral Nutrition

This review describes innovations in providing parenteral nutrition. New research on protein substrates such as arginine and glutamine is discussed as well as potential improvements in providing lipids. The use of hormonal supplementation to improve nutrition is also addressed, with sections on both growth hormone and insulin-like growth factor. Mattox TW, Bertch KE, Mirtallo JM. Recent advances: Parenteral nutrition support. *Ann Pharmacother* 1995;29(2):174-80.

Smoking Cessation

Unfortunately, many pediatricians may find this review article useful in their practices. The pharmacology of nicotine is described as well as both nonpharmacologic and pharmacologic methods to support smoking cessation. An algorithm of treatment options and a cost comparison of nicotine patches are presented. An editorial and several brief introductory articles, including one on

teen smoking, are also contained in this issue. Haxby DG. Treatment of nicotine dependence. Am J Health-Syst Pharm 1995;52(3):265-81.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee on 2/24/95:

1. Pegaspargase injection (Oncaspar) was approved for use in pediatric leukemic patients being treated under POG protocols. This product is L-asparaginase conjugated to a polyethylene glycol carrier. It was designed to cause fewer hypersensitivity reactions than L-asparaginase, but its benefit has not been clearly demonstrated.
2. Butorphanol intranasal spray (Stadol NS) was approved for use in patients who can't tolerate oral medications and who do not have IV access (such as outpatients with migraine headaches). This is a mixed agonist-antagonist with activity at sigma receptors. As you may recall, this group of opioids is associated with a higher incidence of adverse CNS effects (hallucinations, delirium) and therefore is not recommended in children. In addition, patients who have developed tolerance to opioids may experience withdrawal if this agent is administered.

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