Another Look at Adverse Drug Reactions

Article · March 2012

CITATIONS
0

READS
50

1 author:

Michael A Fotis
Northwestern University
32 PUBLICATIONS **1,000** CITATIONS

SEE PROFILE

Another Look at Adverse Drug Reactions

by Michael A. Fotis, Manager Drug Information and Use Policy, Residency PGY1 Director, Northwestern Memorial Hospital

Introduction

Adverse Drug Reactions (ADRs) are common, overlooked, expensive, serious and underreported. Most of our understanding of adverse reactions is based on anecdotal information reported on a voluntary basis. ADR reports are commonly incomplete, and even inaccurate.[1-3]

Evaluating publications for ADR risks

In theory, a published clinical trial provides the best opportunity for a clinician to obtain a systematic analysis of a medication's ADR risk. In practice, the reader should proceed cautiously and carefully to evaluate the provided safety information as outlined in Table 1. The first step is to determine if ADRs are even reported in the publication, as a surprising percentage of study reports (15-50%) do not even report ADRs.[4-7] Every year Bill Budris, Drug Information Pharmacist at Northwestern Memorial Hospital and I lead several teams of fourth professional year students on drug information advanced practice experiences (APPEs) through research projects which are often presented at the ASHP Midyear Clinical Meeting. Last year one of the projects examined recent publications to note the extent and quality of ADR reporting and these findings were presented at the 2011 ASHP Midyear Clinical Meeting in New Orleans.[8] **Table 1** summarizes the results of our study[8] and previously published reports on this topic.[4-7] The frequency of missing ADR information in these reports was surprising. In addition, specialty publications and high impact journals appeared to both be affected by lack of thorough ADR reporting. The fact that reviewers and editors accept these papers for publication further surprised us. It should not be assumed that the absence of safety reporting is evidence of safety, and publications that exclusively report on favorable information offer little value to the reader.

When safety is reported, the methodology should be carefully assessed and the reader should note how adverse effects were identified by the investigators. Spontaneous reporting and other "don't ask" methods of passively collecting ADRs may overlook important information. A high quality publication will follow a systematic approach to collect safety information and use an active adverse event surveillance system based upon a validated checklist. The publication should report results of pre-specified objective safety endpoints, while accounting for all patient withdrawals because of ADRs. Unfortunately, only about 20% of papers report adverse effects using this systematic approach, and the usefulness of data from many clinical trials is compromised either by the absence of ADR reporting or by weak methodology.[9] The final step is to verify that the subjects in the study are similar to the patients you plan to treat. Age, gender, race, severity of illness, other illnesses and medications are important study exclusions to note.

Table 1 – Summary of studies that reviewed reporting of ADRs in journal articles			
Study	**Specialty**	**Number of articles reviewed**	**Number of articles that did not report any ADRs (%)**
Gandhi et al[8]	High impact journals	306	55 (18)
Loke YK et al[4]	High impact journals	185	25 (14)
Nieto A et al[6]	Allergy and immunology	504	244 (48)
de Vries TW et al[5]	Pediatrics	107	24 (22)
Breau RH et al[7]	Urology	152	43 (28)

Assessing ADR risk from clinical trial reports

The design of drug research studies limits their ability to detect rare yet serious adverse events. These studies are designed to see if the medication can show benefit under optimal circumstances, and a study with fewer exclusion criteria would be needed in order to show benefit and safety under the usual conditions of clinical care.[10] Unfortunately, the cost and time necessary to conduct studies with this high level of external validity would be prohibitive, so most studies limit their enrollment to only the healthiest of eligible patients.[11,12] These groups of included study patients often are not representative of the population that will receive the medication after marketing.[11] Jadad et al found that patients with multiple chronic diseases were excluded from 63% of published randomized controlled trials, and only 2% of evaluated trials made it clear that they included patients with multiple chronic diseases.[13] Other limiting factors inherent in the design of these studies include the small numbers of patients receiving the study medication and their short duration. Thus the structure of a drug development trial including use of a controlled setting, documented patient compliance, short term and intermediate outcomes, and low external validity is very different from what is encountered in clinical practice and risk of harm may be much higher in the clinical setting when compared to the research setting.[10,14]

The risk of an ADR is magnified when a drug is prescribed for an off-label indication or in a dose that exceeds that recommended in the official labeling. This enhanced risk can be evaluated by a safety specification study that compares the frequency of reported ADRs between patients receiving a medication for its labeled indications to the ADRs seen when the medication is used off-label. This information provides an early warning about types of patients or situations that are at a particularly high risk for ADRs.[11] Safety specification studies might also warn about drug-drug or drug-diet interactions and special risks for female patients, children, elderly, or other types of patients that are often excluded from registration trials. Both comparative effectiveness and safety specification studies offer new research opportunities for pharmacists interested in identifying and preventing ADRs.

For these reasons clinicians should exercise caution before prescribing a recently approved medication, particularly when using it outside of the inclusion criteria used for the drug registration trial. Caution is especially needed when the registration trial was conducted with strict inclusion and exclusion criteria and therefore represented only a narrow portion of the population under optimal health conditions.[14-16] Rather than succumbing to marketing-based claims such as "a novel compound" or having "a unique mechanism of action", prescribing decisions should be guided by first giving consideration to medications that have an established track record of safety and efficacy.[14] **Table 2** summarizes the questions to consider when assessing a clinical trial report for ADR information.[9]

Addressing these issues at Northwestern Memorial Hospital

At Northwestern Memorial Hospital, we have changed the structure of the evaluations we prepare for our Pharmacy and Therapeutics (P&T) Committee. When we evaluate the literature, we also note if adverse drug reac-

Table 2 – Evaluating clinical trial reports for ADR information*

- Are adverse events actually reported?
- Passive or active surveillance used to identify adverse event (AE)?
- Is a validated checklist available?
- Are pre-specified objective endpoints reported?
- Are patient withdrawals because of adverse events reported?
- Are AEs reported in the abstract, methods, and results section?
- Discussion includes a balanced discussion of harms and benefits?
- Is there external validity?

* Adapted from Ionnidis PA et al.[9]

tions were reported, identify the adverse outcome measured, and the method(s) of data collection. If a formulary proposal is for an off-label use of a medication, we carefully evaluate the inclusion and exclusion criteria for the registration trials and try to identify potential risks proactively. Finally, if medications are being used off-label in groups of patients at high risk for ADRs, we work with our pharmacy students and PGY1 residents to conduct safety specification analyses. Thus far, all of the practice changes have been endorsed by the P&T Committee at our institution.

References

1. Bennett CL, Nebeker JR, Yarnold PR, Tigue CC, Dorr DA, McKoy J. Evaluation of serious adverse drug reactions: a proactive pharmacovigilance program (RADAR) vs safety activities conducted by the Food and Drug Administration and pharmaceutical manufacturers. *Arch Intern Med.* 2007 May 28;167(10):1041-9.
2. Committee on Quality of HealthCare in America. To err is human: building a safer health system. Kohn LT, Corrigan JM, Donaldson MD, eds. Washington, DC: National Academy Press; 1999.
3. Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br J Clin Pharmacol.* 1998;45:301-8.
4. Loke YK, Derry S. Reporting of adverse drug reactions in randomised controlled trials—a systematic survey. *BMC Clin Pharmacol.* 2001;1:3.
5. de Vries TW, van Roon EN. Low quality of reporting adverse drug reactions in paediatric randomised controlled trials. *Arch Dis Child.* 2009;95:1023–6.
6. Nieto A, Mazon A, Pamies R, Linana JJ, Lanuza A, Jiménez FO et al. Adverse effects of inhaled corticosteroids in funded and non-funded studies. *Arch Intern Med. 2*007;167(19):2047–53.
7. Breau RH, Gaboury I, Scales CD Jr, Fesperman SF, Watterson JD, Dahm P. Reporting of harm in randomized controlled trials published in the urological literature. *J Urol.* 2010 May;183(5):1693-7.
8. Gandhi S, TenBarge A, Caraher K, Winters-Williams L, Fotis M. Shining the light on drug safety. ASHP Connect . November 2011. [Online] http://connect.ashp.org/ASHP/ASHP/Go.aspx?c=ViewDocument&DocumentKey=3e9737cd-f8a8-4f00-9ef5-fb793d7da9c8 *(may require ASHP Connect sign-in)*
9. Ionnidis PA, Evans S, Gotzsche P, O'Neill R, Altman D, Schulz K, Moher D. Better Reporting of harms in randomized trials: An extension of the CONSORT statement. *Ann Intern Med.* 2004;141:781-8.
10. Schumock, G. Comparative effectiveness research: Relevance and applications to pharmacy. *Am J Health Syst Pharm.* 2009 Jul 15;66(14):1278-86.
11. Goldman S, Hoffman J, Klein C, Dombrowski S. Discussion Guide on Risk Evaluation and Mitigation Strategies. [Online] 2011. [Cited: September 28, 2011.] www.remsupdates.org
12. U.S. Food and Drug Administration. Managing the risks from medical product use: creating a risk management framework: report to the FDA commissioner from the Task Force on Risk Management. Rockville, MD: May 1999. http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm180325.htm [Online]
13. Jadad AR, To MJ, Emara M, Jones J. Consideration of multiple chronic diseases in randomized controlled trials. *JAMA.* 2011 Dec 28;306(24):2670-2.
14. Schiff GD, Galanter WL, Duhig J, Lodolce AE, Koronkowski MJ, Lambert BL. Principles of conservative prescribing. *Arch Intern Med.* 2011 Sep 12;171(16):1433-40.
15. Largent EA, Miller FG, Pearson SD. Going off-label without venturing off-course: evidence and ethical off-label prescribing. *Arch Intern Med.* 2009;169(19):1745-7.
16. Rhodes NJ, Wozniak EM, Caraher K, TenBarge A, Fotis M. Comparison of on-label and off-label use of dabigatran etexilate at Northwestern Memorial Hospital. ASHP Connect November 2011 [Online] http://connect.ashp.org/ASHP/ASHP/Go.aspx?c=ViewDocument&DocumentKey=36c8e1ee-527e-4058-9320-82a3c3b1e063 *(may require ASHP Connect sign-in)* ▪