Adverse Drug Reactions

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PROLOGUE
This lecture comprises the first hour of a 100-minute lecture in the first of a three-part sequence required in the advanced pathophysiology and pharmacotherapeutics course for our PharmD students at Northeastern University. This first course covers topics on clinical laboratory analysis and interpretation, and cardiac, renal, and hepatic organ systems with emphasis on treatment of principle disease states likely to be encountered by students in practice. While the first portion of the material herein is presented in a traditional didactic style, patient cases are discussed in class to “practice” identifying and evaluating ADRs during this lecture as well as throughout the year on a regular basis. Only three of five patient cases are presented here. Furthermore, ADRs are incorporated into all lecture topics and patient cases presented in the weekly conference session in hopes to strengthen problem-solving skills. The identification of the various types of drug reactions and the treatment and management of reactions is covered extensively in another lecture.

LEARNING OBJECTIVES
1. Discuss the economic impact, culture, and definitions of ADRs.
2. Discuss the elements and the role of the pharmacist in detecting, reporting, evaluating, managing, educating, and preventing ADRs.
3. Discuss the role of the FDA’s ADR reporting program and their role in post-marketing surveillance compared to in-hospital reporting, and other settings.
4. Identify strategies that will assist pharmacists in capturing as well as preventing ADRs.
5. Identify an ADR and assign probability for its occurrence using the Naranjo algorithm.

EVALUATION OF STUDENT PERFORMANCE
Written and oral quizzes and examinations evaluate student performance of recognizing and documenting ADRs. At the beginning of the course, a single ADR will be presented in a patient case with a single attached algorithm to be completed. As the quarter progresses, the complexity of the cases escalates. So, in some instances a case will have four ADRs, perhaps a single drug causing four reactions, or four separate drugs causing four reactions. Another scenario is a patient case may have a single ADR, but the examination will have four attached reporting forms. If incorrect ADRs are reported, the student is penalized heavily. During oral examinations, there exists at least one ADR in which the student must identify. The purpose is to have the student become better at recognizing, evaluating temporal relationships, and developing consistency in ADR reporting.

INTRODUCTION
Epidemiology
Adverse drug reactions (ADRs) are the most frequently reported cause of adverse events during hospitalization accounting for nearly 20 percent (1-4). Of these more than 14 percent result in serious disability (3). ADRs fall under the umbrella of adverse drug events (ADE)(2). It is estimated that up to 20 percent of all hospitalized patients suffer at least one ADR during their stay (1). In the United States, medication related deaths (discounting illicit use) top 120,000 annually which accounts for <1 percent (1-3). At first glance, deaths due to adverse reactions appear negligible but on the contrary, the enormity of all drug doses utilized dwarfs the magnitude (small numerator in relation to a very large denominator). Only more recent have we begun to appreciate that ADRs in the ambulatory and community setting are unknown as well as patient outcomes to these events. Thus, pharmacists can and should play a greater role in this area.

Economic Impact
The astronomical costs associated with ADRs are contributing and adversely impacting the direction of health care. ADRs cause a mean increase in hospital stay of almost two days which results in costs of nearly $3,500 (1997 dollars) per patient (5,6). This amount does not account for those costs associated with malpractice nor the cost of injury to the patient. The national yearly cost of drug related morbidity and mortality was recently estimated at $76.6 billion with $47 billion related to hospital admissions associated with drug therapy (1,5,6). To place this in perspective, the cost of all diabetes care has been estimated at about $45 billion(1).

Culture
ADRs are vastly underreported (2). There exist several plausible reasons for low reporting. First, historically physicians have not embraced the need to report ADRs (7). Their fear stems from a possible negative association or “stigma” of poor practice that could potentially set the stage for a malpractice suit. Although great strides have been made to move away from this mentality, there still exists many that have a concern. Second, the failure to recognize an ADR is also common (8-10). Patients being placed on drug therapy after drug therapy to “treat” new complaints lends support to this. Poly pharmacy is where pharmacists have the opportunity to play a critically

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important role. Third, there is also the failure to report ADRs simply due to laziness and lack of follow-up(2,7). Depending of the circumstances surrounding an ADR, sometimes the patient’s course must be followed over a long period or if the patient leaves a particular facility, effort is required to track the patient’s course(11,12). Pharmacy practitioners remain the principle recorders of ADRs(2,15). ADE documentation, specifically ADRs is just one of many responsibilities that you will encounter as a pharmacist.

ADVERSE DRUG REACTIONS

Definitions

Many definitions exist for describing an ADR. The World Health Organization (WHO) has vehemently tried to establish a definition, universal documenting, assessing, probability assignment so that a commonality exists worldwide(14). The purpose being to identify trends or serious reactions in an efficient and expedient fashion. Additionally, the WHO has recently directed great efforts towards helping developing countries initiate ADR reporting systems so that in addition to prescription medications, herbal remedies or other nontraditional therapies are reported. In the United States, several definitions exist which stems from “fine-tuned” definitions of an ADR (see Appendix)(14-16).

Briefly, other terms that warrant defining are side effect and drug allergy. A side effect is a dose-related and predictable reaction to a drug. A drug allergy is a non-dose related and unpredictable effect of a drug (17,18). Other terms that commonly cause confusion are listed in the Appendix(14,16,20,21).

Reporting

ADR reporting is important when new agents with limited clinical experience enter the marketplace. Initial reports of adverse reaction have taken up to seven years for trends to begin to appear in the literature(9,22,23). Thus, efforts in post-marketing surveillance have helped in the ability to recognize trends earlier(23,24).

The need for reporting ADRs should be considered as important as treatment and overall care of the patient. The Food and Drug Administration (FDA) legally mandates that pharmaceutical manufacturers report all ADRs(24,25). In instances of death, unexpected, or serious reactions, ADRs must be reported to the FDA within 15 days(9). In order to consolidate and streamline the ADR reporting process, the FDA initiated the Medwatch program(21). This program enables practitioners to use a single telephone number to report events. ADR information for Medwatch may be submitted via: (i) prepaid U.S. mail form (FDA form 3500); (ii) calling WATTS 24-hour toll free telephone number (1-800-FDA-1088); (iii) facsimile (1-800-FDA-0178); or (iv) modem (1-800-FDA-7737).

In comparison, ADRs reported by health professional occur on a voluntary basis. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires hospitals to have written procedures for ADR reporting, evaluating, and monitoring(7,12,26,27). In addition, the JCAHO requires institutions to have a means in which ADRs can be utilized to improve patient care. Typically, the hospital’s pharmacy and therapeutics (P and T) committee reviews monthly summaries of ADRs(7,28). The reporting of ADRs occurring in other settings is still unclear. This is the case with ambulatory or community settings. However, the impetus is to devise means in which to capture ADRs in non-traditional arenas.

Monitoring

ADR reporting usually occurs retrospectively. This is simply because we do not realize the event of a reaction until it occurs. Thus, monitoring in this manner is sometimes limited. Concurrent ADRs, enables practitioners to manage and monitor the event in an ongoing fashion in hopes to minimize the reaction and associated costs. The importance of retrospective or concurrent monitoring can not be overemphasized. The reason is that these alert “signals” to practitioners regarding adverse reactions occurring in drug therapy(14).

Prospectively monitoring ADRs is preferred. This way reactions could be potentially avoided or minimized and by doing so cost can be more effectively avoided. Prospective monitoring often occurs in response to a series of serious or unusual reactions that signals us to pay closer attention to monitoring of drug therapy. The pharmacist has an opportunity to greatly impact patient care by foreseeing potential ADRs that can be avoided.

Communicating

Another key aspect surrounding the occurrence of an ADR is communication. It is important to share with all health care practitioners the details surrounding the undesired event. Communication should include a complete history of past and current drug and medical history with particular scrutiny on temporal relationships. Furthermore, any current or previous treatments for reactions should also be recorded. All this information needs to be documented in the patient’s medical record and communicated to all involved in the patient’s care including the pharmacist, pharmacy, and the patient.

Educating

It must not be overlooked that the patient needs to be educated about the circumstances surrounding any ADR suffered. Patients need to be informed, as their role in health care is also important. They should be informed of the type of adverse reaction and drugs to avoid in the future. Depending on the nature and the severity of the reaction, a Medic-Alert bracelet may be helpful. Educating other practitioners in other practice areas or colleagues is also helpful so that everyone can be on a prospective alert. This is particularly important when an event occurs with a new agent or an usual or rare reaction.

Documenting

It is crucial to thoroughly evaluate all aspects surrounding an ADR in order to assign appropriate probability for occurrence and to avoid inaccuracies in causality assignment(29,30). Other aspects important in recording ADRs are documentation of causality, severity, and outcome (see Appendix)(31). Documentation of ADRs must thoroughly represent complete and accurate findings.

Assigning Probability

In order to provide continuity with documenting the probability of an ADR occurring, many tools have been developed to assess the probability for occurrence(21,32-34). Most tools available have not been tested for reliability. Furthermore, many tools are extremely cumbersome to use and difficult to understand. The ideal tool would be one that is reliable, easy, and quick to use to assess the probability of an ADR.

The Naranjo algorithm is one means to assign the likelihood of a drug causing an untoward event (Figure 1)(34). This simple ten-item questionnaire uses specifically assigned numerical values to arrive at an overall total score for proba-
Fig. 1. Adverse drug reaction report form (adapted from reference 34).

Prevention

Many ADRs are preventable(35-37). Examples include drug therapy in excessive doses, known drug-drug, or drug-disease, or drug-food interactions, or inappropriate drug administration. The latter case is a classic example of a drug misadventure, which is also a type of ADE.

In order to potentially avoid ADRs, an understanding of those likely to suffer an ADR needs to be examined(3,22,38,39). Evaluate the patient's age. Elderly patients, regardless of current health status, have age-related decline in organ function. Thus, decreased hepatic metabolism or renal clearance may predispose them to ADRs. Likewise, neonates may have prematurely developed organ systems, which may subject them to ADRs. Patients with underlying disease states, such as human immunodeficiency virus (HIV), tend to experience a greater incidence of ADRs compared to the general population.

Besides patient factors, various aspects of drug therapy may place a patient at risk for experiencing an ADR(35). Intravenous administration has the potential for causing ADRs such as injection site irritation, phlebitis, extravasation, and quick systemic effects not seen with oral administration. Immediate release product formulations also have the potential for faster systemic effects not usually seen with sustained release preparations. Extended duration of drug therapy, depending on the drug’s characteristics has the potential for causing ADRs compared to a short duration of therapy. Additional factors that may place patients at risk for ADRs are patients who receive drug therapy from multiple prescribers, consume nonprescription medications without the knowledge of health care practitioners, and are infrequently or inadequately monitored.

PATIENT CASES

Example 1

The patient is a 52-year-old woman who presents to the emergency department with an erythematous rash and audible wheezing. She presented to the clinic 2 days ago for a second evaluation for elevated blood pressure. She was started on benazepril 5 mg po qd. After taking the second dose, she
noticed a rash on her torso and upper arms. Shortly thereafter, she began experiencing difficulty breathing as well as some facial swelling. Her past medical history was notably only for high blood pressure for 4 years that was previously controlled by diet and exercise. She has no history of tobacco use, or alcohol use. She has no known drug or food allergies. Her current medication is benazepril, and she has not taken any prescription or non-prescription medications for more than 3 weeks. On physical exam, she is a well developed, well nourished woman in moderate distress. Her vital signs are as follows: blood pressure 100/70 mmHg, heart rate 80 beats per minute, respiratory rate 30 beats per minute, and afebrile. She weighs 64 kg and is 5 feet 4 inches. On examination, she had notable edematous swollen face, inspiratory and expiratory wheezing, and a red, maculopapular rash on trunk and upper extremities. She was alert and oriented. Her serum chemistries and complete blood count were within normal limits.

Analysis. Has the patient suffered an ADR? Did a drug precipitate a reaction in this patient? Let’s complete an ADR on this patient of benazepril induced angioedema.

Example 2

The patient is a 38 year old white woman who was admitted to the medicine service for evaluation of headache, chest pain and fatigue for the past three days.

PMH: Chronic renal failure on CAPD x 4 years
Past history of pulmonary embolism x 2 in the past four years
High blood pressure x 10 years, currently controlled
Osteoarthritis of both knees

ALL: indomethacin (GI upset)

SOCIAL: ETOH-wine, occasional with dinner

VS: BP 100/50 HR 40’s RR 28 T 38.5

PMH: H/O endocarditis xl (last episode 3 years ago)
Mitral valve replacement (porcine) 6 years ago
Asthma x 15 years, about 1 ER admission yearly
Atrial fibrillation x 1 year
High Blood Pressure x 20 years
Dyspepsia x 2 weeks
DM x 1 year

Meds: (In ER and home)
digoxin 0.25 mg po QD x 1 year
atenolol 50 mg po BID x 1 year
amiodarone 400 mg po TID (started in ER to complete a 10 gm load)
verapamil 80 mg po TID x 1 week
hydrochlorothiazide 25 mg po BID x 15 years
omeprazole 40 mg po HS x 2 weeks
ECASA 325 mg po QD x 15 years
Theophylline 200 mg po BID (has not taken the last 2 days)
atorvastatin 10 mg po QD x 4 months
Tylexol with codeine No. 3 po Q4 to 6 hours prn pain x 2 weeks
spirinolactone 50 mg po QD x 12 years
MOM 30 ml po QD prn constipation (about twice a week)
Tylexol 325 mg po Q6 hours prn usual aches and pains (about twice a week)
cimetidine 200 mg po QD (takes twice a week)
glyburide 10 mg po QD

Analysis. Has the patient suffered an ADR? Did a drug precipitate a reaction in this patient? Complete an ADR on this patient.

Example 3

The patient is a 65 yo woman who is admitted to the hospital for mild SOB, DOE, myalgia of arms and legs, general malaise, anorexia, nausea, vomiting x 1 episode, and vision changes x 12 hours.

HPI: Approximately 2 weeks ago, the patient had her left upper molar removed secondary to decay. Unfortunately, the procedure was complicated by a crack below the gum line which required unplanned surgery to remove several imbedded chips. Besides having localized tooth and jaw pain, the patient has felt increasingly “out-of it” the last 2 days.

PMH: Brother - suffered ischemic stroke at age 60, recently had defibrillator (AICD) placed
Sister - 68 alive and well
FH: Mother - died of MI at age 44
SH: (+) smoking 2 ppd x 39 years
(+ ETOH 1 six pack daily
FH: Mother - died of MI at age 44
Father - died of ischemic stroke at age 55
Sister - 68 alive and well
Brother - suffered ischemic stroke at age 60, recently had defibrillator (AICD) placed

Physical Examination
VS: BP 100/50 HR 40’s RR 28 T 38.5
HT 5’6” WT 65 kg

LABS: Na 136 CI 95 K 5.1 HCO3 23
BUN 30 Scr 2.9 Mg 2.5 ALB 4
INR 1.1 PT 105 Fe 83 TIBC 300
Hgb 9 Hct 21 MCV 109 MACHE 34
Folate 1.2 B12 100

ECG: sinus tachycardia with no significant changes from previous ECG strip taken 2 months ago.

Analysis. Has the patient suffered an ADR? Did a drug precipitate a reaction in this patient? Complete an ADR on this patient.

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Analysis. Has the patient suffered an ADR? Did a drug precipitate a reaction in this patient? Complete an ADR on this patient.

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Analysis. Has the patient suffered an ADR? Did a drug precipitate a reaction in this patient? Complete an ADR on this patient.

Analysis. Has the patient suffered an ADR? Did a drug precipitate a reaction in this patient? Complete an ADR(s) on this patient.

CONCLUSION
ADRs and ADRs contribute to the everincreasing costs of health care(6). Pharmacists play an important role in recognizing, evaluating, monitoring, communicating, and documenting ADRs. It is as important to correctly identify an ADR as it is to not incorrectly identify an ADR(29,30). It is essential not to incorrectly attribute medical conditions, which may resemble classic or notorious adverse reactions, to the use of drugs. Adverse reactions, particularly those that are serious or rare, should prompt careful and thorough evaluation(40). Prior to final reporting, follow-up can further establish appropriate assignment of probability and outcome. The pharmacist plays a vital role in ADR documentation.

References

APPENDIX

Definitions (14-16)

W.H.O.: Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Karch and Lasagna: Any response to a drug which is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose.

ASHP: Any undesirable or unexpected event that requires discontinuing a drug, modifying a
dose, prolonging hospitalization, or administering supportive treatment (modifications expand on the above definitions in order to include drug overdoses and drug interactions).

**Classification terminology** (14,16,19-21)
- **Unavoidable:** Known effects of the drug that occur routinely as part of the pharmacological spectrum of activity
- **Untoward:** An extension of the pharmacological effect as a result of excessive dosage, or a direct toxic effect on an organ system
- **Idiosyncratic:** Rare adverse reactions, not dose-related, cannot be anticipated
- **Hypersensitivity:** Allergic manifestation of an ADR involving immune mechanisms

**Severity** (16,19-21)
- **Minor:** No antidote, therapy or prolongation of hospitalization required
- **Moderate:** Required a change in drug therapy, specific treatment, or an increase in hospitalization by at least one day
- **Severe:** Potentially life-threatening, caused permanent damage or required intensive medical care
- **Lethal:** Directly or indirectly contributed to the death of the patient

**Causality** (16,19-21,34)
- **Definite:** Reaction resolved when the drug was discontinued and recurred when the patient was rechallenged with the drug.
- **Probable:** Reaction resolved when the drug was discontinued and the reaction is not be explained by an existing clinical condition.
- **Possible:** Suspected drug was continued or numerous drugs were discontinued simultaneously.
- **Doubtful:** There is no reasonable temporal relationship between the reaction and the