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Adverse Drug Reactions for the Emergency Physician: Part I

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What do the following cases presenting to the emergency department (ED) have in common: a young patient who presents with syncope while undergoing treatment for pharyngitis; an epileptic patient who presents with an exfoliative rash; and an elderly patient who presents with confusion and agitation after starting treatment for depression? The answer is that these acute symptoms could be caused by adverse drug reactions. With the variety of patients presenting to the ED, the multitude of drugs prescribed to and used by these patients, the common use of herbal and over-the-counter medications, and the potential use of drugs of abuse, it is not surprising that adverse drug reactions are common. Thus, it is important for emergency physicians to be aware of the possibility of adverse reactions and to recognize their serious potential. These next two issues of Emergency Medicine Reports *discuss both the common and potentially life-threatening adverse*

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drug reactions that can and do present to the ED.
—J. Stephan Stapczynski, MD, Editor

Introduction

Adverse drug reactions (ADRs) are commonly encountered in the emergency department (ED), and are an important consideration in the evaluation and management of every patient. Recognition of ADRs is especially important, as a patient may need to avoid the drug in the future to prevent a more severe reaction on re-challenge. An ADR may be obvious, as in when the patient presents with symptoms that began after taking the medication, or when the onset occurs in the ED. The presentation also may be more subtle, leaving the discovery of the medication relationship up the astute physician. Additionally, interactions between new medications being prescribed and medications the patient is already taking must be always be considered by the practitioner before patient discharge. This article discusses the most common and relevant ADRs in emergency medicine.

Epidemiology

The World Health Organization (WHO) defines an adverse drug reaction as any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. Adverse reactions of drugs are an important cause of morbidity and mortality.[1,2] In 1994 and again in 2000, it was estimated that more than 2 million hospitalized patients in the United States experienced a serious ADR.[3] A serious ADR is defined as one that is lethal, life-threatening, results in permanent or significant disability, requires or prolongs hospitalization, results in a congenital anomaly, or requires intervention to prevent permanent impairment or damage (www.fda.org/medwatch). From this data, it was calculated that 106,000 deaths were caused by ADRs, which could account for up to 4.6% of recorded deaths from all causes in the United States in the same time period.[1] These numbers make ADRs the fourth most common cause of death in the United States, ahead of pulmonary disease, AIDS, accidents, and diabetes. In a 2001 study of geriatric admissions to a hospital, ADRs accounted for 6.7% of the reasons for admission.[4] A similar study in adults in England showed an admission rate for ADRs of 6.5%. In this study, the projected annual cost of these ADRs was $847 million.[5] The annual cost of ADRs in the United States is estimated to be $136 billion.[6]

The safety of drug prescribing has become a highly visible topic in adult medicine but much less attention has been focused on neonates, infants, children, and adolescents.[7] In 2001, a meta-analysis of 17 prospective studies found that overall incidence of ADRs in hospitalized children was 9.53%, with severe reactions accounting for 12.29% of the total. These results show that ADRs in children are also a significant public health issue.[8]

Thus, adverse drug reactions are an important cause of morbidity and mortality and a significant public health concern in both adults and children. Methodologically sound drug surveillance studies are necessary for effective promotion of safer use of drugs in all ages.[8]

The Pharmacology of Adverse Drug Reactions

ADRs generally are divided into predictable (Type A) and unpredictable (Type B).[9] Type A reactions comprise the majority of ADRs, and may be due to the primary mechanism of the drug or to a secondary or minor mechanism. Most are not lethal or life-threatening and most are identified prior to marketing and are noted on the package insert.

Type B reactions include idiosyncratic reactions, immunologic or allergic reactions, and teratogenic or carcinogenic effects of a drug. They rarely are predictable or avoidable and generally are unrelated to the known pharmacologic mechanisms of a drug. They occur due to individual susceptibility. As such, they are unrelated to the dose or route of administration. Type B ADRs generally are uncommon but are the most serious or life-threatening. Organ systems most commonly affected include the liver, skin, and blood, and sometimes the kidney and the nervous system.[10]

Pre-marketing trials are not large enough to identify every potential ADR, particularly the rarest ones, such as drug-induced liver disease. Thus, that a medicine is deemed "safe" for marketing does not imply that the drug is completely harmless.

Polypharmacy is an important risk factor for ADRs. Studies have shown that the risk of ADRs increases exponentially when the patient is taking four medicines or more.[11] Decreased elimination of a drug, as in kidney, liver, or heart disease, and from

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genetic polymorphism, is another important risk factor. Both polypharmacy and decreased elimination are found in the populations most at risk for ADRs: the elderly and the sick neonates.

Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angioedema

Angioedema results from an inflammation of the deeper layers of the dermis or the subcutaneous tissue. It most commonly involves the perioral, periorbital, and oropharyngeal tissues, but has been reported to include the bowel, resulting in recurrent abdominal symptoms.[12,13] Angioedema from ACEIs is related to elevated bradykinin levels, since ACE is needed for the degradation of bradykinin to inactive products.[14] The accumulation of bradykinins results not only in the angioedema, but also in the cough seen with ACEI treatment.

Angioedema has been seen with angiotensin receptor blockers, although most patients tolerate these medications well after an episode of ACEI angioedema.[15,16] A multitude of other pharmaceuticals and food items also have been reported to cause angioedema.[17] In a recent study, 64% of cases of acquired angioedema were due to ACEIs. In this same study, most patients with angioedema were women and were African American.[18] Most patients presented within 2 months of starting the therapy, but some had been treated for up to 5 years.[18] Another study of more than 12,000 patients using enalapril showed a rate of angioedema of 0.68%.[19]

The management of ACEI angioedema consists of withdrawing the offending agent. Although it is not a true allergic reaction, the management is identical to that of anaphylaxis: IV corticosteroids, IV antihistamines, and the cautious use of epinephrine. Airway compromise is a concern with angioedema, and patients should be intubated early if there is the potential for, or suggestion of, problems with airway patency. In several case reports, fresh frozen plasma has been effective in the treatment of angioedema.[20]

Gastrointestinal Bleeding and Non-steroidal Anti-inflammatory Drugs

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is one of the two leading causes of peptic ulcers, and peptic ulcer disease is the leading cause of gastrointestinal (GI) bleeding.[21] In the United States, it is estimated that 100,000 patients are admitted every year for NSAID-induced GI bleeding, with an annual death toll of about 16,500.[22]

According to prospective data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), 13 of every 1000 patients with rheumatoid arthritis and 7.3 per 1000 patients with osteoarthritis who take NSAIDs for one year have a serious GI complication.[23] The mortality rate of NSAID-induced upper GI bleeding in hospitalized patients is estimated to be about 5-10%. Although the estimated mortality is relatively low in the general population, it has to be remembered that NSAIDs are used widely as both prescription and over-the-counter medications. Thus the actual incidence of GI complications related to NSAIDs may be grossly underestimated.[23]

Some established risk factors known to be associated with the development of NSAID-associated gastritis include advanced age, history of ulcers, concomitant use of steroids, higher doses of NSAIDs (including use of more than one NSAID), concomitant use of anticoagulants, and serious systemic disorders. Some possible risk factors include concomitant infection with *Helicobacter pylori*, cigarette smoking, and consumption of alcohol.[23]

NSAIDs have direct toxic effects on the gastroduodenal mucosa, resulting in mucosal injury. There also are some indirect effects through the formation of active hepatic metabolites and decreases in mucosal prostaglandins.[24] The clinical symptoms of NSAID-induced gastrointestinal injury include a combination of subepithelial hemorrhages, erosions, and ulcerations that often is referred to as "NSAID gastropathy."[25]

The management of NSAID-induced GI injury begins with removal of the offending agent. Less toxic analgesics, such as acetaminophen (Tylenol, Panadol), should be substituted for NSAIDs when possible. Once NSAID therapy is discontinued, treatment aimed at healing the erosions or ulcer should be started. Any of the available H2-receptor antagonists, proton pump inhibitors, and sucralfate (Carafate, Sulcrate) are reasonable options.

Due to the prevalence of NSAID-related GI complications, attempts to prevent the actual injuries are always recommended. The best way to prevent mucosal injury is to avoid the prolonged use of NSAIDs and to substitute an agent less toxic to the gastroduodenal mucosa, such as acetaminophen, salsalate (Disalcid, Salflex, Amigesic), or magnesium salicylate (Trilisate). Nevertheless, a potent NSAID commonly is preferred by physicians. Two strategies have been used to improve their safety: the administration of concomitant medication to protect the gastroduodenal mucosa from injury and the development of safer anti-inflammatory agents. Proton pump inhibitors, histamine blockers, and misoprostol (Cytotec) all have been used to prevent and to heal mucosal injury.[26,27] Highly selective cyclooxygenase-2 (COX-2) inhibitors and NSAIDs containing nitric oxide decrease the likelihood of injury to the GI mucosa while at the same time maintaining the anti-inflammatory properties.[23]

Anticonvulsant Hypersensitivity Syndrome (AHS)

AHS is the term given to the constellation of signs and symptoms related to adverse reactions to the aromatic anticonvulsants, namely phenytoin (Dilantin), carbamazepine (Tegretol, Carbatrol, Epitol), and phenobarbital (Luminal).[28-30] Recently, lamotrigine (Lamictal) also has been been implicated.[31] A hypersensitivity syndrome related to each drug was noted shortly after their individual introductions, which has led to multiple previous names for this syndrome (such as DRESS—drug reaction, eosinophilia, and systemic symptoms). The term AHS was first coined in 1988 to recognize that all of these anticonvulsants can cause the constellation of symptoms.

AHS is a rare adverse event (1/1,000 to 1/10,000) characterized by fever, rash, and internal organ involvement (liver, kidney, central nervous system [CNS], lungs), usually with lymphadenopathy, that begins 1-8 weeks after treatment initiation. It is not dose-related and can recur if the drug is re-started.[28-30]

Fever is present in almost all cases and usually is mild but may reach 40°C.[30] The rash, described as an "exanthem with or without pruritus," is seen in almost 90% of patients.[29] There may be associated periorbital or facial edema (which suggests a worse prognosis,) with tonsillitis, pharyngitis, oral ulcers, or conjunctivitis.[29] A rash that is exfoliative suggests Stevens-Johnson syndrome or toxic epidermal necrolysis, which is discussed later. Lymphadenopathy is seen in two-thirds of patients, and may involve any area of the body.[29] The anticonvulsants have been associated with pseudolymphoma, and at times this term has been erroneously used interchangeably with AHS.[30]

The most commonly affected organ is the liver (30-94% of cases).[28,29] The degree of liver involvement can vary from a mild transaminitis to fulminant hepatic necrosis, and correlates with mortality.[28] Other findings in AHS include eosinophilia, hematologic abnormalities, and nephritis.[28] Less common findings include myalgias, arthralgias, rhabdomyolysis, pneumonitis, and thyroiditis,[29] which results in hypothyroidism approximately 2 months after presentation.[30]

With phenytoin and carbamazepine, patients may experience an initial rash days after the first dose. The rash is a mild erythema which spares the face, and responds to a reduction in dose or a temporary discontinuation of the medication.[29] If patients present with this rash, a work-up to exclude AHS, including laboratories, is indicated. However, discontinuing the medication is indicated if fever or any laboratory abnormalities are present.[30]

The exact cause of AHS is unknown. The common link between carbamazepine, phenytoin, and phenobarbital is an aromatic benzene ring in its structure. This is metabolized to arene oxide, which displays cytotoxicity and triggers an immune response.[28] It is postulated that there are genetic differences in metabolism of this toxic intermediate, which may account for the familial tendency to sensitivity toward the aromatic anticonvulsants.[30]

There is no gold standard for diagnosis of AHS. The diagnosis is based on history and clinical examination, coupled with laboratory abnormalities.[29] Because of this, and the potential for mortality if AHS is missed, the clinician must have a high index of suspicion for the disease.

The mainstay of treatment is discontinuing the offending drug and providing supportive care. The use of systemic corticosteroids, IV immunoglobulins, and antihistamines is controversial but recommended by some authors in the more severe cases.[30-32] Attention still should be given to seizure control in the epileptic patient, and selection of the appropriate agent should be undertaken in consultation with the patient's neurologist.

Due to the high degree of cross-reactivity among the aromatic anticonvulsants, patients should not be switched to another medication in this class. Family members of patients with AHS should be warned, and may want to undergo testing prior to starting any of the drugs in this class.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

In 1922, Drs. Stevens and Johnson first described the syndrome (SJS) that now bears their name, noting two patients who had been misdiagnosed as having hemorrhagic measles. They had developed a febrile erosive stomatitis and cutaneous eruption of deep red macules, sometimes with necrotic centers, as well as ocular involvement. The term toxic epidermal necrolysis (also known as Lyell's disease) was described in 1956 by Lyell to refer to similar patients with extensive skin necrosis.[33]

SJS and TEN make up a small portion of adverse cutaneous reactions to drugs that affect hospitalized patients.[33,34] They are distinguished from other drug reactions by their potential seriousness and mortality. While there may be agreement on some characteristics of the disease, there are no unifying diagnostic criteria.[35] Generally agreed-upon characteristics are deep red cutaneous macules with confluence and desquamation in some parts. These lesions desquamate under lateral pressure (positive Nikolsky sign).[36,37] Nearly 90% of patients will have mucosal involvement,[33-36] and 85% will have ocular involvement.[33] Patients may have fever and influenza-like symptoms 1-2 days before appearance of the rash.[33,35,37] These symptoms generally start within 1-4 weeks of initiating a new drug.[33,35]

SJS and TEN do not have a racial, age, or gender predilection, and they have an incidence of 0.4-1.2 cases/million person/year (TEN), and 1.2-6 cases/million person/year (SJS).[33] Patients at an increased risk are those with HIV, lupus, the elderly, and bone marrow transplant recipients.[33]

While at one point considered distinct entities, currently SJS and TEN are thought to be a continuum of the same disease. The diagnosis of SJS is made if less than 10% of the skin surface area is involved, and TEN is used if more than 30% of the skin is involved. Between 10 and 30% is referred to as SJS/TEN overlap.[33,34,36-38] Histopathologically, both entities appear identical,[34] revealing epidermal detachment with intact dermis.[33]

The pathophysiology of SJS and TEN remains unclear, but is thought to be immune-mediated.[33] The offending drugs and their metabolites may bind to keratinocytes, inducing the immune system to act against the skin.[37]

Etiology

While a very rare side effect of therapeutic drug usage, drugs are found to be the cause of more than 95% of TEN cases, and about 50% of SJS cases.[33] There are more than 100 compounds associated with this disease. The most common are antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs (e.g., piroxicam [Feldene] and meloxicam [Mobic]), and allopurinol (Zyloprim).[33-36] Significantly rarer, non-drug causes have been identified and generally produce a milder form of the disease.[34]

Complications

Complications of SJS/TEN generally are related to the sloughing of the mucosal layer of the gastrointestinal (GI), respiratory, and ocular systems. Sloughing of the tracheobronchial epithelium is the most concerning, as patients may develop bronchial obstruction, produce bronchial casts, or develop Acute Respiratory Distress Syndrome (ARDS).[35,37] The loss of intestinal epithelium contributes to dehydration, electrolyte imbalances, and renal complications.[35,37] The ulceration of oral mucosa and

Table 1. Risk Factors for Drug-Induced QT Prolongation

PHARMACOLOGIC FACTORS	INDIVIDUAL FACTORS
• Medication with intrinsic blockade of cardiac potassium efflux (particularly I_{kr})	• Female gender
• Concomitant administration of multiple medications known to prolong QT interval	• Electrolyte disturbances (hypokalemia, hypomagnesemia)
	• Bradycardia < 50 beats per minute
	• Structural heart disease (cardiomyopathy, congestive heart failure, ischemia)
• Supratherapeutic or toxic dosing of medication, resulting in high medication levels	• Renal dysfunction
	• Hepatic dysfunction
• Concomitant administration of a QT-prolonging medication with an agent inhibiting its metabolism, resulting in high medication levels	• Individual genetic "repolarization reserve" (mutations affecting cardiac ion currents)
• Concomitant administration of medications resulting in electrolyte disturbances (eg, potassium wasting diuretics) and medications known to prolong the QT interval	
• Rapid intravenous infusion of agent known to prolong the QT interval	

Data adapted from De Ponti F et al, and Owens, et al.[47,48]

esophageal epithelium make maintaining PO nutrition painful.[37] Finally, the loss of the outer layer of the cornea and sclera result in significant ocular complications, and is the most common long-standing morbidity.[35]

Treatment

The cornerstone of treatment for SJS/TEN is discontinuing any offending drugs and providing meticulous supportive care. Any drug started in the past month should be considered a suspect.[33] The supportive care required is similar to but less intense than that required for thermal burns. Because of this, many patients are transferred to a burn unit.[33] Compared to burns, these conditions require less intravenous (IV) fluids, as there are few large blisters and little subcutaneous edema due to a lack of vascular damage.[36,37] Debridement generally is not recommended, as it increases the extent of skin damage.[37] Additionally, avoid all sulfa products and involve ophthalmology early.[35,37]

All other treatment modalities are controversial. Those that have been proposed and studied to some degree are steroids, IV immunoglobulins (IG), cyclophosphamide (Cytoxan, Neosar), cyclosporine (Neoral, Sandimmune, Gengraf), plasmapheresis, hemodialysis, thalidomide (Thalomid) (due to presence of TNFa in the skin), and N-acetylcysteine (NAC) (Mucomyst, Parvolex).[33,37] The most literature and controversy surrounds the use of steroids. Steroids are used to stop the progression of the disease, however they may increase the risk of infection, and infection is the leading cause of death in these patients.[35,37]

Outcome

The mortality for SJS is less than 5%; however, for TEN it is more than 30%.[33,36] Death in these patients usually is due to sepsis.[33,35] Risk factors for mortality seem to be more related to underlying, preexisting diseases than to the drug involved in causing the syndrome.[33] Other risk factors include degree of skin detachment, advanced age, and internal organ involvement.[33]

Since the dermis is generally not involved, re-epithelialization is not a problem.[37] Epidermal regrowth usually occurs in approximately 3 weeks.[33,37] The affected skin usually heals without scars, however synechiae of eyelids and in the anogenital region may occur.[35-37] Patients may have alopecia or permanent nail loss.[37] Up to 35% have residual ocular problems.[33]Any identified causative drug should be strictly avoided in the future.[37]

Phosphodiesterase-5 Inhibitors (PDE5) and Nitrates: Hypotension

Sildenafil, Vardenafil, Tadalafil. The PDE5 inhibitors made their appearance on the market for the treatment of erectile dysfunction with the introduction of sildenafil (Viagra) in April of 1998.[39] This drug became an overnight success, with more than 10 million U.S. men using the drug in its first 5 years.[39] Other drug companies soon followed with vardenafil (Levitra) and tadalafil (Cialis).

The interaction of PDE5 inhibitors with organic nitrates—nitroglycerin, isosorbide dinitrate (Isordil, Sorbitrate, Dilatrate, Cedocard), isosorbide mononitrate (ISMO, Monoket, Imdur), amyl nitrite, amyl nitrate—was known prior to its introduction onto the market, and use of nitrates remains the only absolute contraindication to the drugs' use.[40]

While PDE5 inhibitors themselves can cause a slight, generally asymptomatic drop in blood pressure, the combination of PDE5s and nitrates can produce significant hypotension.[40] This is particularly important as there is significant overlap in the risk factors for erectile dysfunction and the risk factor for medical conditions for which a patient may receive nitrates, such as angina and congestive heart failure.

Nitrate-PDE5 inhibitor mediated hypotension occurs due to an overlap in mechanism of the two drugs. Nitric oxide (NO) released by the vascular endothelium stimulates guanylate cyclase, which increases the production of cGMP. The cGMP then acts on the vascular smooth muscle to cause relaxation.[41,42] Nitrates increase the production of cGMP. PDE5 inhibitors, as their name implies, inhibit phosphodiesterases, which break down cGMP, particularly PDE5, which is the predominant PDE in the corpus cavernosum.[41,42] The combination of nitrates and PDE5 inhibitors result in a vast excess of cGMP, producing sig-

nificant vascular smooth muscle relaxation.[41]

Among the PDE5 inhibitors, tadalafil is notable for its longer half-life. A combination of tadalafil and nitrates resulted in statistically significant drop in standing blood pressure after sublingual nitroglycerin 0.4 mg up to 24 hours post-tadalafil ingestion in a recent study.[43]

Because of this potentially significant interaction, the current ACC/AHA guidelines recommend avoidance of nitrates in patients who have used sildenafil or vardenafil in the preceding 24 hours, and 48 hours for tadalafil.[44] The best treatment for this interaction is prevention. Prior to administering any nitrates, any caregiver, including those in the pre-hospital environment, should ask the patient whether they have taken any PDE5 inhibitors in the past 24 or 48 hours. If so, nitrates should be withheld. This includes withholding the amyl nitrite pearls and the sodium nitrite injection included in the cyanide antidote kit. Patients taking nitrates chronically should not use PDE5 inhibitors.

There is no antidote for the PDE5 inhibitors. Should a patient become hypotensive due to receiving nitrates after using a PDE5 inhibitor, the hypotension should be treated with intravenous fluids, vasopressors, and an intra-aortic balloon pump (IABP) if necessary.

Prolonged QT Syndrome

It is well recognized that many conditions may cause prolonged or abnormal repolarization resulting in a long QT interval. This in itself is not particularly concerning, however these patients are at increased risk for malignant arrhythmias, particularly torsade de pointes (TdP).[45] Many medications that were initially known to prolong QT interval were antiarrhythmics, with quinidine as the most commonly implicated agent. However, many other medications are now also associated with QT prolongation or TdP. They include psychiatric medications, antihistamines, anti-infectives, and others such as arsenic and methadone. (*See Insert.*)[46]

Some patients may be at greater risk for developing prolonged QT than others because of a genetic predisposition to arrhythmias. (*See Table 1.*) Inherited defects of cardiac ion channels have variable penetrance, and not every carrier will manifest changes on a screening ECG. However, this patient population may be at increased risk when exposed to agents that block potassium channels and "unmask" their genetic predisposition to QT prolongation and arrhythmias.

The exact incidence of drug-induced TdP in the general population is largely not known. Although there has been an increase in spontaneous case reports in the literature, the absolute total number remains very low. It has been suggested that the system of voluntary reporting underreports the true incidence of serious ADRs by a factor of possibly 10.[45]

In practice, adverse effects of QT prolonging drugs can be prevented by not exceeding the recommended drug dose; avoiding their use in patients with pre-existing heart disease or risk factors mentioned above; and avoiding these drugs in patients with history of previous ventricular arrhythmias and/or electrolyte imbalance such as hypokalemia. The concomitant use of medications that can prolong QT and/or result in electrolyte imbalance also should be avoided.[45]

The management of patients who have drug-induced TdP includes treating the arrhythmia, removing the offending agent, repleting potassium if necessary, and infusing magnesium (1-2 grams IV). Although magnesium will not decrease the QT interval, it will increase the activity of the magnesium-dependent sodium/potassium pump, leading to the reuptake of potassium ions in exchange for sodium ions.[46] Other treatments for TdP include administration of IV isoproterenol (Isuprel) as well as possible insertion of an overdrive pacemaker. Pacing at rates from 90-140 beats/minute may be required to suppress the dysrhythmia. Both overdrive pacing and isoproterenol have had intermittent success and should be used only in cases of acquired long QT syndrome; in patients with congenital long QT syndrome, increased heart rate may promote the arrhythmia. Isoproterenol may be used in patients with significant bradycardia but should be avoided in patients with poor left ventricular function or severe coronary artery disease. Defibrillation also has been used with variable success.[46]

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Physician CME Questions

121. Adverse drug reactions are accountable for what percentage of patient deaths in the United States?
    A. Fewer than 3.6%
    B. Up to 4.6%
    C. More than 5.5%
    D. 2-3%

122. The mechanism for ACEI-angioedema involves the accumulation of bradykinin.
    A. True
    B. False

123. Which of the following has *not* been identified as a cause of SJS/TEN?
   A. Anticonvulsants
   B. Sulfonamides
   C. NSAIDs
   D. Antihypertensives

124. Which organ system is involved in the most common long-standing morbidity of SJS/TEN?
   A. Skin
   B. Cardiovascular
   C. Eyes
   D. Gastrointestinal

125. Which of the following is a known risk factor for drug-induced QT prolongation?
   A. Concomitant administration of multiple medications known to prolong QT interval
   B. Concomitant administration of a QT prolonging medication with an agent inhibiting its metabolism, resulting in high medication levels
   C. Concomitant administration of medications resulting in electrolyte disturbances and medications known prolong the QT interval
   D. Rapid intravenous infusion of an agent known to prolong QT intervals
   E. All of the above

126. Which of the following treatments is the best way to prevent gastrointestinal mucosal injury?
   A. Antacids
   B. Milk
   C. Naproxen
   D. NSAID avoidance

127. Which of the following is generally *not* recommended in the treatment of SJS/TEN?
   A. Transferring the patient to a burn referral center
   B. Debridement
   C. Early involvement of ophthalmology
   D. Discontinuance of suspected drugs

128. Which of the following is *not* a risk factor for developing NSAID-associated gastritis?
   A. Concomitant use of steroids
   B. Concomitant use of anticoagulants
   C. Young age
   D. Higher doses of NSAIDs

129. A patient who uses tadalafil (Cialis) presents to the ED with chest pain suggestive of ischemia. Before administering sublingual nitroglycerin, you must confirm that he has not taken tadalafil within which timeframe?
   A. The past 4-6 hours
   B. The past 6-12 hours
   C. The past 12-24 hours
   D. The past 24-48 hours

130. What is the most common cause of death in patients who develop TEN?
   A. Dehydration
   B. Hypokalemia
   C. Myocardial infarction
   D. Sepsis
   E. Respiratory failure

CME Answer Key

121. B; 122. A; 123. D; 124. C; 125. E; 126. D; 127. B; 128. C; 129. D; 130. D

In Future Issues: **Adverse Drug Reactions, Part II**

Emergency Medicine Reports CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Adverse Drug Reactions, Part I

Drugs that Can Prolong QT Interval and Torsade de Pointes

Antiarrhythmic drugs	**Type 1A (TdP reported in all):** Quinidine (Quinaglute, Quinalan, Quinate, Quinidex, Quinora) Procainamide (Procanbid, Pronestyl) Disopyramide (Norpace, Rythmodan) **Type 1C (increase QT by prolonging QRS interval):** Encainide (Enkaid) Flecainide (Tambocor) **Type 3 (TdP reported in all):** Amiodarone (Cordarone, Pacerone) Sotalol (Betapace, Rylosol, Sotacor) d-Sotalol Bretylium (Bretylol) Ibutilide (Corvert) Dofetilide (Tikosyn)	**Antihistamines**	Terfenadine (Seladane) (TdP reported, withdrawn in the USA) Astemizole (Himanal) (TdP reported) Diphenhydramine (Benadryl, Allerdryl, Allernix) (TdP reported) Hydroxyzine (Vistaril, Atarax) Ebastine (Evastel) Loratadine (Claritin) Mizolastine (Mizollen, Mistamine)
		Antimicrobial and antimalarial drugs	Erythromycin (Eryc, E-mycin, Ery-Tab, Erybid, Erythromid) (TdP reported) Clarithromycin (Biaxin) (TdP reported) Ketoconazole (Nizoral) Pentamidine (Pentam, NebuPent, Pentacarinat) (TdP reported) Quinine Chloroquine (Aralen) (TdP reported) Halofantrine (Halfan) (TdP reported)
Calcium channel blockers	Prenylamine (Segontin) (TdP reported, withdrawn) Bepridil (Vascor)(TdP reported, withdrawn) Terodiline (Micturin) (TdP reported, withdrawn)		Amantadine (Symmetrel, Endantadine) (TdP reported) Sparfloxacin (Zagam) Grepafloxacin (Raxar) (TdP reported, withdrawn in the UK and USA)
Psychiatric drugs	Thioridazine (Mellaril) (TdP reported) Chlorpromazine (Thorazine, Largactil) (TdP reported) Haloperidol (Haldol) (TdP reported) Droperidol (Inapsine) (TdP reported) Amitriptyline (Elavil, Venatrip) Nortriptyline (Aventyl, Pamelor) Imipramine (Tofranil) (TdP reported) Desipramine (Norpramin) (TdP reported) Clomipramine (Anafranil) Maprotiline (Ludiomil) (TdP reported) Doxepin (Sinequan, Zonalon) (TdP reported) Lithium (Eskalith, Lithobid, Lithonate, Lithane, Carbolith, Duralith) (TdP reported) Chloral hydrate (Somnote, Aquachloral Supprettes) Sertindole (Serlect, Serdolect) (TdP reported, withdrawn in the UK) Pimozide (Orap) (TdP reported) Ziprasidone (Geodon)	**Serotonin agonists/ antagonists**	Ketanserin (Vulketan) (TdP reported) Cisapride (Propulsid, Prepulsid) (TdP reported, withdrawn in the UK and USA)
		Immunosuppressant	Tacrolimus (Prograf) (TdP reported)
		Antidiuretic hormone	Vasopressin (Pitressin, ADH, Pressyn) (TdP reported)
		Other agents	Adenosine (Adenocard) Organophosphates Probucol (Lorelco, Lesterol) (TdP reported) Papaverine (Pavabid, Vasal) (TdP reported) Cocaine

Data adapted from Yap et al
* This list is not comprehensive

Risk Factors for Drug-Induced QT Prolongation

PHARMACOLOGIC FACTORS	INDIVIDUAL FACTORS
• Medication with intrinsic blockade of cardiac potassium efflux (particularly I_{kr})	• Female gender
• Concomitant administration of multiple medications known to prolong QT interval	• Electrolyte disturbances (hypokalemia, hypomagnesemia)
	• Bradycardia < 50 beats per minute
	• Structural heart disease (cardiomyopathy, congestive heart failure, ischemia)
• Supratherapeutic or toxic dosing of medication, resulting in high medication levels	• Renal dysfunction
	• Hepatic dysfunction
• Concomitant administration of a QT-prolonging medication with an agent inhibiting its metabolism, resulting in high medication levels	• Individual genetic "repolarization reserve" (mutations affecting cardiac ion currents)
• Concomitant administration of medications resulting in electrolyte disturbances (eg, potassium wasting diuretics) and medications known to prolong the QT interval	
• Rapid intravenous infusion of agent known to prolong the QT interval	

Data adapted from De Ponti F et al, and Owens, et al.[47,48]

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