REVIEW

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Unusual effects of common antibiotics

ABSTRACT

Antibiotics are widely prescribed and have a generally favorable safety profile. Common adverse effects such as rash and diarrhea are well recognized, but less common ones may go unrecognized. This review highlights rare but potentially lethal complications associated with antibiotics.

KEY POINTS

Piperacillin-induced encephalopathy and seizure can occur on a continuum, with progressive dysarthria, tremor, and confusion culminating in tonic-clonic seizures.

Monocycline-induced lupus can present as myalgia, arthralgia, serositis, constitutional symptoms, and a positive antinuclear antibody titer. The effect is not dose-dependent.

Acute tubular necrosis has been linked to cephalosporins and tetracyclines. Crystal nephropathy has been reported with quinolones and sulfonamides.

QT-interval prolongation is a class effect of quinolones and is more likely to occur in patients with pre-existing QT prolongation, electrolyte abnormalities, organic heart disease, or bradycardia, or in women.

doi:10.3949/ccjm.86a.17050

A 60-YEAR-OLD MAN is admitted for respiratory failure following a massive myocardial infarction. He develops ventilator-associated pneumonia and is treated with cefepime and vancomycin. Three days later, he develops prolonged atypical absence seizures.

What caused these seizures? The neurologist thinks it might be the cefepime. Do you agree?

Antibiotics are widely used in the United States, with 269 million courses of oral therapy prescribed in 2011.[1] Adverse effects such as rash are well known, but rare effects such as seizure, hypoglycemia, and hypoxemia may not be immediately attributed to these drugs.

In this article, we review less-recognized but potentially serious adverse effects of antibiotics commonly prescribed in the United States. We have structured our discussion by organ system for ease of reference.

NERVOUS SYSTEM

The potential adverse effects of antibiotics on the nervous system range from encephalopathy and seizure to nonconvulsive status epilepticus.

Encephalopathy and seizure

Encephalopathy has been reported with penicillins, cephalosporins, sulfamethoxazole-trimethoprim, quinolones, and oxazolidinones such as linezolid.[2,3]

Seizures are known to occur with penicillins, cephalosporins, carbapenems, and quinolones.[2–4] For cephalosporins, these effects are more common at higher doses, in elderly patients, and in patients with renal impairment. Carbapenems are associated with seizure activity in elderly patients.[2–4]

Encephalopathy and seizure can also occur on a continuum, as is the case with piperacillin-induced encephalopathy, with progressive dysarthria, tremor, and progressive confusion culminating in tonic-clonic seizures.[2]

Nonconvulsive status epilepticus

Nonconvulsive status epilepticus, marked by prolonged atypical absence seizures, has complicated the use of penicillins, quinolones, clarithromycin, and cephalosporins, specifically cefepime.[2,3,5] Diagnosis can be difficult and requires clinical awareness and confirmation with electroencephalography.

Class-specific neurologic effects

Certain antibiotics have class-specific effects:

Tetracyclines: cranial nerve toxicity, neuromuscular blockade, and intracranial hypertension.[2]

Sulfamethoxazole-trimethoprim: tremors and psychosis, with visual and auditory hallucinations.[6]

Macrolides: dysequilibrium and potentially irreversible hearing loss.[2]

Quinolones: orofacial dyskinesia and a Tourette-like syndrome, with a higher incidence reported with newer quinolones.[7]

Linezolid: optic and peripheral neuropathy[2]; neuropathy can be persistent and can lead to loss of vision. The package insert recommends monitoring visual function in patients taking linezolid for more than 3 months and in any patient reporting visual symptoms.[8]

Linezolid is also associated with serotonin syndrome when combined with a drug that potentiates serotonergic activity, most commonly selective serotonin reuptake inhibitors. The syndrome is characterized by a triad of cognitive or behavioral changes, autonomic instability, and neuromuscular excitability such as spontaneous clonus.[9]

Metronidazole: optic and peripheral neuropathy, in addition to cerebellar toxicity and central nervous system lesions on magnetic resonance imaging of the brain. In a series of 11 cases of cerebellar toxicity, most patients presented with ataxia and dysarthria associated with high total doses of metronidazole, and in most cases, magnetic resonance imaging showed resolution of the lesions upon discontinuation of metronidazole.[10]

Neurologic effects of macrolides include dysequilibrium and irreversible hearing loss

HEMATOLOGIC AND RHEUMATOLOGIC EFFECTS

Agranulocytosis has been associated with beta-lactams, in most cases with prolonged exposure. In one report, the average exposure before onset of agranulocytosis was 22 days for nafcillin and 25 days for penicillin. For penicillins, more than 50% of cases involved high daily doses.[11]

Likewise, most episodes of vancomycin-induced neutropenia were reported to occur after 20 days of therapy.[12]

In another study, most cases of drug-induced anemia were due to ceftriaxone and piperacillin.[13]

Drug-induced thrombocytopenia has been described with penicillins, cephalosporins, sulfonamides, and vancomycin[14] and is a well-recognized effect of linezolid. The syndrome of drug reaction with eosinophilia and systemic symptoms, a severe and rare adverse reaction, has been reported with minocycline, sulfamethoxazole, and vancomycin.[15]

The tetracycline minocycline has been reported to cause drug-induced lupus and polyarteritis nodosa-like vasculitis.[16] Drug-induced lupus presents as myalgias and arthralgias, serositis, constitutional symptoms, and positive antinuclear antibody titers. The effect is not dose-dependent. Penicillin, cefuroxime, and nitrofurantoin have also been implicated.[16]

Kermani et al[17] described 9 cases of polyarteritis nodosa, in which 5 patients (56%) had systemic involvement including renal artery microaneurysm, mononeuritis multiplex, and mesenteric vasculitis, and some of these patients also had cutaneous involvement. All patients had positive antineutrophil cytoplasmic antibody in a perinuclear pattern. The median time from start of the minocycline to symptom onset was 9 months, and the median duration of use was 2 years.

Quinolones have also been reported to cause fatal hypersensitivity vasculitis.[18,19]

CARDIOVASCULAR SYSTEM

Macrolides and quinolones have been reported to cause QT-interval prolongation and torsades de pointes. The risk is greatest when a macrolide is co-administered with a CYP3A4 inhibitor.

Of the macrolides, azithromycin is the safest, as clarithromycin and erythromycin are more likely to cause QT prolongation.

While QT prolongation is a class effect of quinolones, there is variability within the class. Ciprofloxacin is thought to be the safest in terms of cardiovascular adverse effects.[20] In addition, Owens and Nolin[20] reported that quinolone-associated QT prolongation was more likely to occur in patients with pre-existing QT prolongation, electrolyte abnormalities, organic heart disease, and bradycardia, and especially in women. Other risk factors for QT prolongation with quinolone use include underlying cardiac disease and advanced age.[21]

Quinolones have also been associated with an increased risk of aortic dissection. The US Food and Drug Administration has issued a warning advising clinicians to avoid quinolones in patients who have aneurysms or are at risk for aneurysms, such as patients with advanced age, peripheral atherosclerotic vascular disease, hypertension and conditions such as Marfan and Ehlers-Danlos syndrome.[22]

DIGESTIVE SYSTEM

Tetracyclines are known to cause esophagitis from direct contact with and disruption of the mucosal lining. Doxycycline is the most frequent offender.[23]

Amoxicillin-clavulanate is the antibiotic most commonly associated with drug-induced liver injury, mainly attributable to the clavulanate component.[24] It is more common in men over age 50 and with prolonged and repeated dosing and is sometimes fatal. Other adverse effects include Stevens-Johnson syndrome, interstitial nephritis, and thrombotic thrombocytopenic purpura.[25]

Cholestatic hepatitis has been reported with penicillins, particularly dicloxacillin, oxacillin, and amoxicillin-clavulanate; cephalosporins; doxycycline; sulfamethoxazole-trimethoprim; macrolides; and ciprofloxacin.[24–26] Hepatocellular injury is linked to amoxicillin-clavulanate and doxycycline. Drug-induced mixed liver injury has been observed with amoxicillin-clavulanate, sulfamethoxazole-trimethoprim and, rarely, cephalosporins.

Liver injury is classified as cholestatic if the alkaline phosphatase level is more than 2 times higher than normal, or if the ratio of alanine aminotransferase to alkaline phosphatase is less than 2; if the ratio is greater than 5, the injury is considered hepatocellular.[24] Mixed liver injury, the most common, is defined as a ratio from 2 to 5.

Nitrofurantoin has also been linked to hepatotoxicity, cirrhosis, and end-stage liver disease, and to death if the drug is continued after the onset of jaundice.[26] Death from liver injury has been reported with amoxicillin-clavulanate, sulfamethoxazole-trimethoprim, and erythromycin, and jaundice indicates a poor prognosis, associated with a 10% mortality rate or need for liver transplant in all patients.[24]

ENDOCRINE SYSTEM

Clarithromycin, sulfonamides, and quinolones are known to precipitate hypoglycemia by interacting with sulfonylureas. A study of Medicare patients age 66 or older who were taking glipizide or glyburide reported that female sex, older age, and a history of hypoglycemic episodes were associated with antibiotic-related hypoglycemia.[27] The odds ratio for hypoglycemia was highest for clarithromycin (3.96), sulfamethoxazole-trimethoprim (2.56), metronidazole (2.11), and ciprofloxacin (1.62) when compared with antibiotics that do not cause hypoglycemia. There was no signal for levofloxacin-mediated hypoglycemia in this series.[27]

RESPIRATORY SYSTEM

Hypersensitivity lung disease has been reported with penicillin, ampicillin, cephalosporins, ciprofloxacin, and sulfonamides including sulfamethoxazole-trimethoprim.[28] The lipopeptide daptomycin has been reported to cause acute eosinophilic pneumonia defined as fever for less than 5 days, pulmonary infiltrates, hypoxemia, and a bronchoalveolar lavage or biopsy study with eosinophils. Daptomycin should be stopped early in these cases, and the patient should not be rechallenged, as the reaction can be deadly.[29]

Daptomycin should be stopped early for acute eosinophilic pneumonia, as it can be deadly

Nitrofurantoin has a long history of hypersensitivity pneumonitis in its acute form and a chronic allergic response. While more widely recognized, nitrofurantoin pulmonary toxicity

is rare, occurring in 1 in 5,000 patients.[30]

RENAL SYSTEM

Acute interstitial nephritis has been reported with penicillins, cephalosporins, macrolides, quinolones, sulfonamides, and vancomycin.[31–33] Acute tubular necrosis has been linked to cephalosporins and tetracyclines. Crystal nephropathy has been seen with quinolones and sulfonamides.

Advanced age is an important risk factor for renal dysfunction from quinolones,[18] and penicillin G has been reported to cause glomerulonephritis.[31]

MUSCULOSKELETAL SYSTEM

Quinolones have been associated with arthropathy or tendinitis at a rate of 1%, including cases of Achilles tendon rupture.[18] The US Food and Drug Administration announced in 2016 that the serious adverse events with fluoroquinolones outweigh the benefits in patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infection, and that they should be used only if there are no other options.[34]

Daptomycin is known to cause elevations of creatine kinase.[34] Weekly monitoring is recommended based on postmarketing data reports of elevations in 2.5% of patients; myopathy is a rarer effect, occurring in 0.2% of patients.[35]

REPRODUCTIVE SYSTEM

Antibiotics have long been reported to interact with oral contraceptives, but the data are not compelling for commonly used antibiotics. The strongest association is with rifampicin, which reduces oral contraceptive efficacy and warrants an alternative mode of contraception.[36]

BACK TO OUR PATIENT

Antibiotics can have serious adverse effects, and it is important for clinicians to be cognizant of this. Our 60-year-old patient who was taking cefepime and vancomycin for pneumonia developed prolonged atypical absence seizures. When the cefepime was discontinued, his mental status improved, and no other seizures were observed.

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