UWTASP
tele-antimicrobial stewardship program

June 29th,2021

Agenda

- *Antibiotic side effects, part 2*
- Case Discussions
- Open Discussion

Antibiotics side effects are common

- Literature suggests up to 2.8% of hospitalization result from drug-interactions

Antibiotic related toxicities lead to many ED visits!

- The prevalence of emergency department visits for adverse drug events in the United States was estimated to be 4 per 1000 individuals in 2013 and 2014. The most common drug classes implicated were anticoagulants, **antibiotics**, diabetes agents, and opioid analgesics.

JAMA. 2016 Nov 22; 316(20): 2115–2125.

Case 1

A 45 yr patient that you are following for long term treatment of chronic MRSA osteomyelitis returns to clinic complaining of decreasing vision of two weeks' duration.

After an initial course of vancomycin, long term suppression with linezolid 600 mg po q12 was begun three months ago.

Four weeks ago numbness and tingling of finger tips lead to a diagnosis of peripheral neuropathy and pregabalin (Lyrica) was started. Two weeks prior when they noted blurring of vision in his left eye.

Case 1: Audience Response

The most likely diagnosis is….

A. vitamin B deficiency
B. CNS syphilis
C. Pregabalin toxicity (anti-seizure drug)
D. Thiamine deficiency
E. Linezolid toxicity

Case 1 Discussion

- Linezolid can cause polyneuropathy and optic neuritis after several weeks or months of use.
  - Loss of color vision
- Hypesthesias and dysesthesias are more prominent in the hands than in the feet.
- Visual loss from optic neuritis is gradual and asymmetrical.
- Stopping the drug can reverse some of the optic neuritis but less often the peripheral neuropathy

Indian J Ophthalmol. 2014 Apr; 62(4): 497–500

Case 1 Discussion

- Linezolid is known for reversible thrombocytopenia/anemia.
- MOA:
  - thrombocytopenia possibly immune-mediated
  - anemia has been ascribed to a chloramphenicol-like mechanism of myelosuppression
  - Onset: 14 days.
- Pts with cancer and neutropenia: myeloid recovery does not seem to be affected with short courses
- Pts with renal dysfunction: increased risk for thrombocytopenia

https://doi.org/10.1128/AAC.00605-19

Signs/Symptoms

The incidence of serotonin syndrome ranges from 0.24% to 4%

Table 1. Hunter Serotonin Toxicity and Sternbach's Criteria[7,8]

Hunter Serotonin Toxicity Criteria	Sternbach's Criteria
Pt. must be receiving a serotonergic agent and meet 1 of the following conditions: spontaneous clonus inducible clonus plus agitation or diaphoresis ocular clonus plus agitation or diaphoresis tremor plus hyperreflexia hypertonia plus temperature >38 °C plus ocular clonus or inducible clonus	Addition of or increase in a known serotonergic agent and at least 3 of the following symptoms: mental status changes (confusion, hypomania) agitation myoclonus hyperreflexia diaphoresis shivering tremor diarrhea incoordination fever Other etiologies (infection, substance abuse, or withdrawal) have been ruled out A neuroleptic agent has not been recently added or increased in dosage prior to the onset of the symptoms

Most common signs: Typically, agitation and tremors are the initial symptoms.

Table 1. Hunter Serotonin Toxicity and Sternbach's Criteria7,8

Ann Pharmacother 2013 Apr;47(4):543-60.
doi: 10.1345

SSRI syndrome –inciting agents

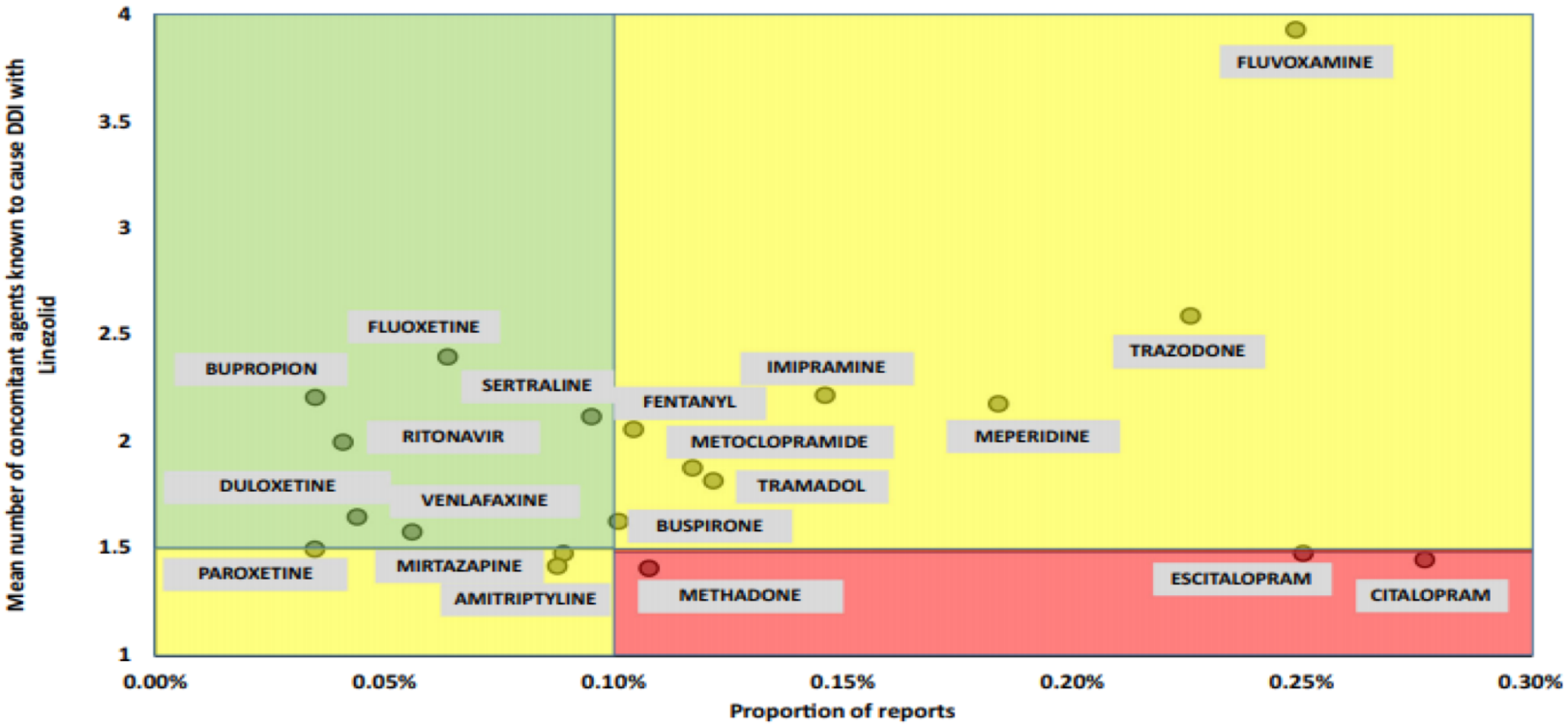

Fig. 2 Scatterplot showing the relationship between the proportion of SS reports (on *x*-axis) and the mean number of DDIs (on *y*-axis) for each serotonergic agent. Threshold values of ≥ 0.1% and ≤ 1.5 were respectively selected for proportion of SS reports and mean number of DDIs, identifying three different SS risk zones (red-zone, high-risk medications; yellow-zone, intermediate-risk medications; green-zone, low-risk medications)

Management: abates in less than 1 to 5 days after discontinuation of offending agents.

European Journal of Clinical Pharmacology (2021) 77:233–239

Case 2 Audience Response

Besides aminoglycosides (gentamicin, tobramycin, or amikacin) which antimicrobial has been associated with hearing loss?

a. Levofloxacin
b. Bactrim
c. Inhaled aztreonam
d. Azithromycin

Case 2 discussion

- Hearing loss, disequilibrium and tinnitus are attributed to macrolides
- Erythromycin can cause sensorineural hearing loss (SNHL)
- Few case reports with clarithromycin
- 31 cases with azithromycin in the last 50 years:
  - Hearing loss occurred within speech frequencies
  - More likely with prolonged exposure and higher doses
  - Most resolved within 2-4 weeks
  - MOA: unknown

Front. Neurol., 09 March 2021
| https://doi.org/10.3389/fneur.2021.652674

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D.,

- Treatment 250mg daily x 1 year
- SNHL confirmed 25% in azihtromycin vs 20% in placebo (p =0.04)
- 34% returned to baseline after discontinuation

Differences in thresholds were compared between measurements made on enrollment and at three months, and between enrollment and 12 months.

Author's state:

"the improvements in hearing that occurred on repeat testing, regardless of whether the study drug was discontinued, suggest that our criteria were too stringent and that the incidence of hearing decrements was overestimated in both groups."

Case 3

60 year old man with h/o kidney transplant (within last month) on prednisone and tacrolimus. He rec'd a 7 day treatment with an "abx" to treat Urinary tract infection.

During her course of the "abx", he presents to ER with left ankle pain with swelling and difficulty ambulating.

Case 3: Audience Response

Which antibiotic class has been implicated tendinopathy and tendon rupture?

A) Macrolides
B) Beta-lactams
C) Fluoroquinolones
D) Glycopeptides

Case 3: Discussion
FQs and tendon injury

- Since their introduction in the 1980s, FQs have been associated with rare reports of tendinopathy including spontaneous rupture, especially of the Achilles tendon.
- the prevalence is low in the general population (0.14–0.4%),
- FDA black-box warning
- Risk factors: > 60 years of age, chronic steroid use, and in patients with kidney, heart or lung transplants.
- median onset of 6 days

- Mechanism: unknown
  - Direct cytotoxic effect musculoskeletal system; chelation of cations

Clinical Drug Investigation (2019) 39:205–213

FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects

"These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. "

We have determined that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis, (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) …."

avoid prescribing fluoroquinolone antibiotics to patients who have an aortic aneurysm or are at risk for an aortic aneurysm, such as patients with peripheral atherosclerotic vascular diseases, hypertension, certain genetic conditions such as Marfan syndrome and Ehlers-Danlos syndrome, and elderly patients.

Case 4

23 yo w/ PMH IVDU and MVR presents with MSSA bacteremia and endocarditis who is being treated with nafcillin and rifampin.

Pt is being treated with nafcillin for the last 2 weeks and you get a call about a 50% drop in WBC.

What are the causes of leukopenia in this patient?

Case 4 Audience Response

What is the most likely cause of the leukopenia in this patient?

a. Nafcillin

b. Rifampin

c. Endocarditis

d. None of the above

Causes of leukopenia

Nafcillin:

- caused neutropenia in 8.4% of OPAT pts when compared to cefazolin (3.3%)
- Caused more side effects
  - rash (13.9% vs 4.2%),
  - renal dysfunction (11.4% vs 3.3%) and
  - LFT abnormalities (8.1% vs 1.6%)
- Nine patients switched to cefazolin without ill effect

Clin Infect Dis 2014:59 (August 1)

Okay to rechallenge with cefazolin

467 patients treated with nafcillin

60 transitioned to cefazolin

Reason for switching:
17 patients due non-IgE hypersensitivity:

- Rash
- immune-mediated nephritis
- isolated eosinophilia
- Immune mediated hepatitis

All but 1 patient tolerated challenge; no pt developed progressive organ dysfunction or worsening of rash

Rifampin: hematologic toxicities

- Thrombocytopenia, leukopenia, and granulocytopenia are relatively common during rifamycin therapy.
- Reversible

- The more severe hematologic complications of rifamycin therapy (e.g., hemolytic anemia, profound thrombocytopenia) are thought to be the result of rifampin-dependent antibodies.

Mandell: Rifamycin chapter

Antibiotics ADRs are real!

Monitoring patients is key!
- have a routine monitoring plan in place for antibiotics

Resources for Antibiotic side effects:

- ✓PubMed
- ✓Colleagues!
- ✓Tertiary Resources
  - ✓UpToDate
  - ✓Mandell's Principles of Infectious Diseases
  - ✓Kucer's : The Use of Antibiotics
- ✓UWTASP

Clinical Infectious Diseases, Volume 68, Issue 1, 1 January 2019, Pages e1–e35, https://doi.org/10.1093/cid/ciy745