ACT III - “A drug without side effects is a drug without effects”

The Bob
Scene 1 - Mr “Sitting Bull”

• What treaty that the white man ever made with us have they kept? Not one……. What law have I broken? Is it wrong for me to love my own? Is it wicked for me because my skin is red? Because I am a Sioux; because I was born where my father lived; because I would die for my people and my country?
Scene 1 - Mr “Sitting Bull”

- 53 y/o male with rash to E.R. Feb 2/07
- PMH: schizophrenia, porcine mitral valve
- Root canal 1 week PTA
- Given clindamycin for 7 days as prophylaxis
  - Vanco, pen and rifampin rashes in past
- Next day red rash begins
- Worsens and spreads over entire body---->to E.R.
Scene 1 - Mr “Sitting Bull”

• Had continued clindamycin throughout
• Initially rash was dark red with violaceous macules and patches studded with petechiae
• Included palms not soles, not mucous membranes
• Hypotensive--received epi, pressors, 12 litres!, steroids, benadryl, ranitidine, ABx
Scene 1 - Mr “Sitting Bull”

- Next day stabilized hemodynamically
- Developed micropustules over forehead, spread all over face then chest then body
- Seen by derm
  - DX: acute generalized exanthematous pustulosis (we knew that!)
  - Bx: superficial dermal acute and chronic inflammatory infiltrate with eosinophils associated with reactive vascular proliferation and red cell extravasation… consistent with AGEP.
“Round up the usual suspects”

Inspector Louis Renaud (Claude Rains) in “Casablanca”

Always suspect the drug!!

“If you don’t think, You don’t look, if you don’t look, You don’t find”
This one is idiosyncratic, but severity related to duration of use and cumulative dose.

Choose the right drug at the right dose for the right duration.
AGEP with pathology
O true apothecary!
Thy drugs are quick.
Thus with a kiss I die.

“‘tis an ill cook who cannot lick his own fingers”
ACT IV: “It’s the ones you don’t see that get you”

• Some drugs have such well-known side-effects that when we monitor so carefully for them, we forget about other potential toxicities.
Scene 1 - Mr Blindside

- 41 year old male schizophrenic with chest pain and ECG changes admitted 27/12/06
- Smoker, prior splenectomy after failed suicide attempt, recent ankle fracture, casted
- Meds: clozapine
- 1 day PTA, acute onset severe sharp central chest pain, worse with deep breathing, associated with SOB and diaphoresis, eased off gradually
- Exam normal, sats normal, routine labs normal except WBC 22.7 neuts 15.3, d-dimer 433, trops neg x3
12-FEB-1965 (41 yr) Male
Vent. rate 111 BPM
PR interval 170 ms
QRS duration 98 ms
QT/QTC 358/486 ms
P-R-T axes S4 -87 20

Room:ER Loc:31

Technician: GENEVIEVE HAMILTON
Test ind: CHEST PAIN

SINUS TACHYCARDIA
LEFT ANTERIOR FASCICULAR BLOCK
ST & T WAVE ABNORMALITY, CONSIDER ANTERIOR ISCHEMIA
INCREASED R/S RATIO IN V1, CONSIDER EARLY TRANSITION OR POSTERIOR INFARCT
ABNORMAL ECG
NO PREVIOUS ECGS AVAILABLE

Referred by: REBECCA COMLEY
Confirmed By: BRAD MUNT, MD
Scene 1 - Mr Blindside

After being seen by internal medicine team and cardiology (including staff), the family medicine resident rotating through CTU makes the diagnosis.
Scene 1 - Mr Blindside

- CXR: slight enlargement of right pulm artery
- Spiral CT: neg, no PE, no right heart strain
- Clozapine level: 4809 (300-2100)
- Nor-clozapine level: 5146 (<2000)
Scene 1 - Mr Blindside

- Dx: clozapine toxicity
- Clozapine d/ced, olanzapine started
- Pain subsided, felt well, ecg unchanged, WBC normalized
- Discharged 2 days later
Scene 2 - Clozapine cardiotoxicity

• Prescribers all aware of agranulocytosis and need for monitoring of CBC
• ECG changes, myocarditis, pericarditis, cardiomyopathy, CHF, MI, autonomic irregularities esp orthostatic hypotension all reported
• Schizophrenic patients on anti-psychotics have much higher cardiac disease rates…is it the disease or the drugs?
Scene 2 - Clozapine cardiotoxicity

- Killian (Lancet 1999): 23/8000 myocardial disease, 6 died, 3 sudden
- Product monograph: 15,600 treated, 9 myocarditis, 3 fatal
- Combined rate 1/14000 patient years, 23% fatal
“99% of all ADRs are dose-related"
Scene 2 - Clozapine cardiotoxicity

- Clozapine-induced QT prolongation seen in cat hearts
- Blockade of cardiac K channels occurs with clozapine in concentration dependent fashion
- May explain pro-arrhythmic activity
Act IV, Scene 3
“It ain’t over ‘til it’s over”
Lawrence Peter Berra
Scene 3—“It ain’t over ‘til it’s over”

- Mr Blindside readmitted Jan 12 with acute psychosis
- MIBI and Echo done in the interim
- MIBI normal
- Echo: dilated RV, RA, PAP 53
- ECG unchanged
NORMAL SINUS RHYTHM
INCOMPLETE RIGHT BUNDLE BRANCH BLOCK
LEFT ANTERIOR FASCICULAR BLOCK
ST & T WAVE ABNORMALITY, CONSIDER ANTERIOR ISCHEMIA
ABNORMAL ECG
WHEN COMPARED WITH ECG OF 08-JAN-2007 07:27,
NO SIGNIFICANT CHANGE WAS FOUND

Technician: SHAHRAM HOUSHYAR

Referred by: C. TAYLOR
Confirmed By: ANDREW IGNAZIEWSKI, MD
Scene 3-“It ain’t over ‘til it’s over”

- Differential includes pulmonary embolic disease vs “idiopathic” pulmonary hypertension, vs OSA
- Do antipsychotics predispose to VTE?
- C Raymond Pharm D., VGH (2003):
  - Association shown in cohort studies, case-control studies
  - One case control study showed OR 7.1 in 30,000 users
  - Association exists, cause-effect unproven
Scene 3-“It ain’t over ‘til it’s over”

- No evidence for VTE (neg spiral CT),
- Workup proceeding with PFTs, sleep studies
- Back on clozapine with close monitoring
“Those who cannot learn from history are doomed to repeat it”

George Santayana
Take Home Points

• Be sure of indications, dosage, duration, and patient characteristics affecting pharmacology
• Factor in risk/benefit of using the drug
• Be aware of drug-drug interactions (OTCs too)
• Anticipate problems and monitor for them
• When symptoms arise in any patient on any drug, consider the drug as potentially the cause
• “You can observe a lot by watching” - Yogi (again!)
• “You could look it up” - James Thurber*
NO
PAT
NO

Don’t sit on that.
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- Greg Bondy
- William Shakespeare
- Yogi Berra
- Bartlett’s Familiar Quotations
- Google.ca
- Apple computers
- Dr. Theodore Seuss Geisel
Disclaimer

- I have not received support from any pharmaceutical firms (in 2007/8 anyway)
- No patients were harmed during the production of this talk
- Any resemblance to any people, alive or dead, is purely coincidence
If, for the sake of a crowded audience you do wish to hold a lecture, your ambition is no laudable one, and at least avoid all citations from the poets, for to quote them argues feeble industry.

Hippocrates
Suggested Drug Info Resources

- Hardcopy: CPS, AFHS drug info, DIR, company monographs etc.
- Subscription-based desktop resources: micromedix, up-to-date etc
- Palm-based: epocrates, dr. drugs
- Websites: Health Canada, FDA etc
- Databases: medline, embase, Cochrane etc
- Internet search engines: google, yahoo etc