Clinical Pharmacology & Toxicology Pearl of the Week

Restarting a medication after an adverse drug event

- ✓ Adverse events from medications is **a common cause** of hospitalization and prolongation of hospitalization
- ✓ Adverse events from medications often go **unnoticed** as medical teams attribute them to the patient's clinical diagnosis
- ✓ The decision to restart a medication following an adverse drug event is complex, requiring a risk/benefit analysis and informed patient consent

Case

- ✓ A 34 y/o male presents to his family doctor with new onset pruritis three weeks after starting phenytoin for a diagnosed seizure disorder. He is found to have a morbilliform rash with slight sloughing. Concerns for DRESS syndrome are raised, and he is sent for blood-work (See PotW on DRESS). He is found to have a WBC count of 15 with eosinophilia. His creatinine is normal, but is ALT/AST are both elevated 4 x ULN with a normal ALP, GGT, and bilirubin. His family physician discontinues the phenytoin and refers him back to his neurologist for reassessment.
- ✓ At the neurology follow-up, his labs have returned to normal and his rash is gone. You are consulted to help decide if the patient can be placed back on phenytoin.

Step 1: Diagnose the adverse drug event

- ✓ Establish a thorough timeline of events and medication history to identify potential causative agents or conditions that may have contributed to the presentation
- ✓ Once a suspect drug (or drugs) are established, **determine likelihood of a drug-reaction having had occurred**.
  - Scoring systems such as Naranjo, Rucam criteria, and Liverpool ADR assessment can be used.
    - Scoring systems include temporal linkage, presence of a mechanism of effect, lack of other likely causes, and pre-existing establishment of the adverse drug event in the literature.

Step 2: Assess benefit of re-introduction of the drug

- ✓ Questions to think about include:
  - Are there alternative treatments with equal efficacy?
  - What is the risk of non-treatment?
    - Define what is an acceptable level of risk from a treatment medication in relation to its expected benefit
  - What are the patient's personal preferences and wishes surrounding their medical care?

Step 3: Assess the risk of re-introduction of the drug

- ✓ Adverse drug reactions are classified into Type A and Type B reactions
  - Type A drug reactions are **dose and time dependent**, and are often **related to the mechanism of action**, or secondary mechanisms of actions of a medication.
  - **Type B drug reactions are not dose dependent**. They are typically immune mediated or idiosyncratic.

Type A Reactions	Type B Reactions
Acetaminophen - hepatotoxicity	Penicillins - Anaphylaxis
Opioids - Hypoxia	Clavulanic Acid – Drug induced liver injury
Sulfonylureas – Hypoglycemia	Carbamazepine – DRESS / SJS
Valproic Acid – Hepatotoxicity / Hyperammonia	Rifampin – Interstitial nephritis
Vancomycin - AKI	Clozapine – Agranulocytosis

Select Examples of Type A and Type B adverse drug reactions

- ✓ Type A reactions are **predictable** and can often be mitigated by pre-treatment, decreasing the dose and exposure, and monitoring drug levels where available.
- ✓ Type B reactions are unpredictable, and are often **more severe on subsequent exposures**
- ✓ Utilize predictive tests when available to help determine degree of risk.

- Ex: Pharmacogenetic testing, skin-allergen testing, anti-drug antibody testing.

Step 4: Can we mitigate the risk of re-introduction of the drug?

- ✓ **Optimize the patient**'s co-existing co-morbidities to decrease contributing and confounding factors towards the adverse drug reaction.
  - Ex: Optimize perfusion and fluid status prior to initiating nephrotoxic medications.
- ✓ **Discontinue medications that can contribute** to the risk of an adverse drug event.
  - Ex: Discontinue medications that interact with metabolism of the offending agent, or that may have synergistic toxicity (nephrotoxic drugs)
- ✓ Pre-treat the patient to prevent certain types of adverse drug reactions.
  - Ex: pre-treat with an antihistamine prior to iron infusion to decrease risk of anaphylactoid reactions
- ✓ In Type A reactions, consider starting with a lower dose

Step 5: Informed Consent

- ✓ When the decision is made to restart a medication, forego treatment, or transition to an inferior medication, informed consent between the patient and the treating team **must be performed**.

Step 6: Restarting the medication (optional)

- ✓ Should be done in a **monitored, hospitalized setting**
- ✓ Begin with the **smallest possible dose** and titrate to effect slowly
- ✓ **Perform routine vitals and focused physical examinations** looking for findings of the adverse event
  - Ex: Rash in DRESS, RUQ pain in drug induced liver injury
- ✓ **Perform focused blood work** looking for the adverse event
  - Ex: LFTs for drug induced liver failure, CBC for agranulocytosis or DRESS, creatinine for AKI
- ✓ Can **consider drug level monitoring** in Type A adverse drug events
- ✓ Discontinue the medication if the reaction occurs again

Back to the case

- ✓ You assess the patient and clinical history, and agree that the patient likely suffered from DRESS secondary to initiation of phenytoin
- ✓ You recommend that the patient not be restarted on phenytoin ever again, as this was a Type B adverse drug reaction with a high risk of reoccurring and being more severe on subsequent exposures.
- ✓ You further recommend against starting any of the aromatic antiepileptic agents due to significant cross-reactivity between them for immune mediated reactions (phenytoin, carbamazepine, oxcarbazepine, and phenobarbital)
- ✓ The neurologist agrees, and transitions the patient to levetiracetam as an outpatient.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

References:

1. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239–45.
2. Stanulovic V, Venegoni M, Edwards B. Intentional rechallenge: does the benefit outweigh the risk? Drug Saf. 2013. doi:10.1007/s40264-013-0020-3.
3. Meyboom, R. Intentional Rechallenge and the Clinical Management of Drug-Related Problems. *Drug Saf* **36,** 163–165 (2013). https://doi-org.cyber.usask.ca/10.1007/s40264-013-0023-0
4. Goldfrank's Toxicologic Emergencies 11th edition. New York: McGraw-Hill, 2006. Internet resource.