Clinical Pharmacology & Toxicology Pearl of the Week

~ Pharmacogenomics and Immune Reactions ~

- ✓ HLAs are proteins on antigen presenting cells responsible for presenting immunogenic proteins and substances, or haptens, to T-cells
- ✓ Genetic variants in HLA genes can increase an individual's risk for severe immune reactions to drugs, including severe cutaneous adverse reactions (SCARs) (ex: DRESS, Stevens-Johnson-Syndrome (SJS))
- ✓ Impaired clearance of drugs can also increase an individual's risk for severe immune reactions.

What factors increase a patient's risk for a hypersensitivity (immune) reaction?

- ✓ Hypersensitivity reactions can be difficult to predict, and have multiple factors that contribute to their pathogenesis
  - Genetic permutations in HLA proteins can increase the risk of hypersensitivity reactions
  - Previous Epstein-Barr Virus, Human Herpes Virus 6 or 7, or cytomegalovirus infection
  - Increased metabolism to more immunogenic metabolites, or decreased clearance of these metabolites
    - Increasing the patient exposure to the immunogenic compounds
  - Underlying immunogenicity of the drug
- ✓ Unfortunately, the presence or absence of any of these factors cannot predict the occurrence of a hypersensitivity reaction. They only influence the underlying risk.

Examples of Clinical Applications

- ✓ **Allopurinol**
  - HLA-B*58:01 genotype is associated with 34-580x increased risk for SCARs.
  - HLA-B*58:01 genotype is found in up to 6% of Asian and less than 1% of European populations.
  - HLA-B*58:01 genotype is an absolute contraindication to allopurinol therapy. Recommendations are to use alternative uric acid lowering pharmacologic and non-pharmacologic therapies.
  - Additional considerations increasing the risk of SCARs in all populations:
    - Higher allopurinol doses
    - Concurrent diuretic use (decreases clearance of allopurinol)
    - Concurrent antibiotic use (decreases clearance of allopurinol)
    - Chronic Kidney Disease (decreases clearance of allopurinol)
- ✓ **Aromatic Anti-epileptics**
  - HLA-B*15:02 genotype is associated with increased risk for SCARs for patients exposed to carbamazepine, oxcarbazepine, lamotrigine phenytoin and fosphenytoin.
  - HLA-A*31:01 genotype is associated with increased risk for SCARs for patients exposed to carbamazepine and oxcarbazepine.
  - HLA-B*15:02 and HLA-A*31:01 genotypes are found in up to 4% of Asian and 2% of European populations.
  - Strong recommendations to avoid **carbamazepine and oxcarbazepine** for patients with HLA-B*15:02 or HLA-A*31:01 genotypes due to increased risk of SCARs. Recommendation to use other anti-epileptics.
  - Strong recommendations to avoid phenytoin and fosphenytoin for patients with HLA-B*15:02 genotype due to increased risk for SCARs. Recommendation to use other anti-epileptics.
    - The risk of cross-reactivity with other aromatic anti-epileptics (Ex: phenobarbital) is unknown although it is generally recommended to avoid these agents as well.

- ✓ **Abacavir**
  - HLA-B*57:01 genotype is associated with increased risk for SCARs.
  - HLA-B*57:01 genotype is found in 3% of European and up to 7% of Central/South Asian populations.
  - HLA-B*57:01 genotype is a contraindication to abacavir therapy. Recommendations are to select an alternative anti-retroviral agent.

Consider HLA testing in high-risk populations prior to prescribing any of the above pharmaceuticals. HLA testing is performed by Alberta Precision Labs and is covered by Alberta Health Insurance.

References:

1. Brunton L, Hilal-Dandan R, Knollmann B, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw Hill Medical; c2018
2. Peck RW. Precision Medicine Is Not Just Genomics: The Right Dose for Every Patient. Annu Rev Pharmacol Toxicol. 2018;58:105-122. doi:10.1146/annurev-pharmtox-010617-052446
3. https://cpicpgx.org/guidelines/
4. Day RO, Graham GG, Hicks M, McLachlan AJ, Stocker SL, Williams KM. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. Clin Pharmacokinet. 2007;46(8):623-644. doi:10.2165/00003088-200746080-00001

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

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