Clinical Pharmacology & Toxicology Pearl of the Week

~ Adverse Drug Reactions ~

Background

- ✓ **An adverse drug reaction (ADR)** is any 'appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product'.

- ✓ Reactions include those that result from intended use, error, misuse, or abuse, unlicensed or off-label use.

- ✓ 5-10% of patients may suffer an ADR at admission, during admission or at discharge.

- ✓ Beyond obvious morbidity and mortality, ADRs have both financial costs to the patient and healthcare system, and negative effect on the prescriber-patient relationship.

- ✓ Frequently implicated medications include: antiplatelets, anticoagulants, cytotoxics, immunosuppressants, diuretics, antihyperglycemics and antibiotics.

Classification

- ✓ Traditionally, ADRs have been classified into two categories:
  - **Type A –** 'dose-dependent' and predictable based on pharmacology of the drug
  - **Type B –** idiosyncratic and not predictable on basis of pharmacology

- ✓ Many types of adverse reactions do not fit within the Type A and B dichotomy, so additional types have been added:
  - **Type C –** both dose and time dependent (i.e., chronic reactions)
  - **Type D –** delayed reactions
  - **Type E –** withdrawal reactions
  - **Type F –** failure of therapy

Assessment

- ✓ In 1981, Naranjo and colleagues developed the Adverse Drug Reaction Probability Scale to help standardize assessment of causality for all adverse drug reactions. While it was designed for use in controlled trials and registration studies of new medications, it is simple to apply and is widely used clinically.

- ✓ **The Naranjo Scale** consists of 10 questions that are answered as either "Yes", "No" or "Do not know". Point values (-1, 0, +1, +2) are assigned to each answer. The total score ranges from -4 to +13.

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total Score:			

Score	Interpretation of Scores
Total Score ≥9	**Definite**. The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.
Total Score 5 to 8	**Probable**. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	**Possible**. The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	**Doubtful**. The reaction was likely related to factors other than a drug.

- ✓ In 2003, Aronson et al., proposed a new classification system for adverse drug reactions, **Dose Relatedness – Timing – Patient Susceptibility (DoTS)**, that considered properties of the reaction (time course of its appearance and its severity) and properties of the affected individual (genetic, pathological, and other biologic differences that confer susceptibility).

Examples of DoTS (dose-time-susceptibility) classification

- Osteoporosis due to corticosteroids: Do—collateral effect; T—late; S—age, sex.
- Anaphylaxis due to penicillin: Do—hypersusceptilbility; T—first dose; S—not understood; requires previous sensitisation
- Hepatotoxicity due to isoniazid: Do—collateral effect; T—intermediate; S—genetic (drug metabolism), age, exogenous (alcohol), disease (malnutrition)

References:

1) Coleman et al. Adverse drug reactions. Clin Med (Lond). 2016 Oct;16(5):481-485.
2) Aronson et al. Joining the DoTS: a new approach to classifying adverse drug reactions. BMJ. 2003 Nov;327:1222-1225.
3) Adverse drug reaction probability scale (Naranjo) in drug induced liver injury. LiverTox. 2019 May.
4) Doherty MJ. Algorithms for assessing the probability of an adverse drug reaction. Resp Med CME2 . 2009;63-67.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultations are also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

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).