1996a(16): Define therapeutic index and briefly outline its significance. Briefly describe also therapeutic ration & use of cardiac/CNS toxicity ratio

Therapeutic Index (TI) = Derived from quantal dose-response curves.

- The margin of safety of a drug measured as the ratio of the median effective dose (ED$_{50}$) and the median lethal dose (LD$_{50}$)

Mathematically expressed as:

$$TI = \frac{LD_{50}}{ED_{50}}$$

**Uses:** Provides a crude indication of the margin of safety of a drug (i.e. the larger the TI, the larger the gap b/n an effective dose and a harmful dose)

- High TI drug: Paracetamol, BZ
  - Can safely give large bolus doses with low frequency
  - Nil plasma monitoring required
- Low TI drug: Theophylline, digoxin
  - In general, need lower doses, ↑freq administration (to limit peak toxicity) (Exception, gentamicin which has toxicity not conc-related)
  - Need to monitor plasma levels of drug (eg phenytoin, digoxin)

**Limitations:**
- LD$_{50}$ not good guide to toxicity in **humans** (measured in animals)→adverse effects limiting use in clinical practice may be overlooked in animal models
- ED$_{50}$ is not definable i.e. it depends on the measure of effectiveness being applied (eg differences in dosage of aspirin to treat a headache vs Rx of RA)
- As it is a ratio based on median doses, it does not take into account *inter-individual variability* with respect to effective or lethal doses or idiosyncratic reactions
- Median values taken from healthy subjects (ED$_{50}$) or animals (LD$_{50}$) therefore may overlook ‘vulnerable’ populations eg paeds, elderly, chronic disease, co-morbidities
- Alterations in dose-response curve characteristics can give a high (safe) TI despite differences in the curves leading to significant overlap in ED and LD (eg ED$_{70}$ = LD$_{20}$)

Therapeutic Ratio (TR) = Comparison of any 2 parameters (eg CVS vs CNS toxicity).

- Commonly used with LA to describe the relationship b/n the drug dose required to produce CNS and CVS toxicity in experimental subjects.
- The higher the number, the larger the gap b/n the doses and the ‘safer’ the LA is (as CNS Sx are 1) easier to manage, 2) less lethal, and 3) precede CVS Sx

The CC/CNS ratio lignocaine = 7
The CC/CNS ration bupivocaine = 3.7, i.e. only 3.7 x the convulsive dose is required to produce a high risk of CVS collapse

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