□ Digoxin

• Digoxin continues to have an important role in the control of CHF and atrial fibrillation, and as a positive inotropic agent in heart failure.

• Digoxin inotropic effect is the basis for its use for treatment in CHF.

• While it's chronotropic effects are the basis for treatment of atrial arrhythmias such as, atrial fibrillation, atrial flutter, and atrial tachycardia.

□ Indication for TDM:

• Narrow therapeutic range with severe toxicity or ADR.

• To distinguish toxicity from inadequate therapy

• impaired renal function to adjust the dose rate.

• Suspected interaction with drugs such as, antacids, amiodarone, oral antibiotics, cholestyramine, cyclosporine, metoclopramide, neomycin, quinidine, spironolactone, verapamil, sulfasalazine etc.

• Due to its incomplete absorption and substantial elimination by the kidney.

• Therapeutic range:

- The commonly reported therapeutic range is 0.5 to 2.0 ng/ml in adults.

• The lower end of the range, 0.5-1 ng/ml is generally used for treatment of heart failure, with levels up to 1.5 ng/ml possibly leading to additional benefits.

• Higher serum Digoxin concentrations are required for the treatment of atrial arrhyth-

mias (0.8 - 1.5 ng/ml), with additional benefits gained in some patients with level up to 2 ng/ml.

- Symptoms of toxicity includes, muscle weakness, GI complaints (anorexia, nausea, vomiting, abdominal pain and constipation), CNS effects (headache, insomnia, confusion, vertigo, and change in color vision), and serious CV effects (bradycardia, premature ventricular contractions and ventricular tachycardia).

Absorption: Digoxin is nearly completely absorbed from the gut but in some patients, absorption may decrease to digoxin inactivation by gut bacteria i.e. Eucobacterium lentum.

- Distribution and metabolism: Digoxin is not

extensively metabolized. Digoxin distributes into lean body tissues but not appreciably into adipose tissues.

• Elimination: Digoxin is excreted largely unchanged in urine with renal clearance near to creatinine clearance.

Sample timing:

• The average Digoxin $t_{1/2}$ in adults with normal function is approximately 2 days. at least 7 days are recommended to attain a steady-state.

• The selection of the optimal time to collect blood for determination of patient's serum Digoxin concentration requires an understanding of the relationship between phar-

macodynamics response and serum concentration time profile.

- The blood sample should optimally be drawn at least 12 and preferably 24 hours after an administration of the dose.
- The potential influence of exercise on Digoxin serum concentration suggests that a period of rest may be needed before blood sampling to avoid an exercise-induced decrease in serum Digoxin concentration.

Specimens collection methods:

- Serum or plasma, anticoagulated with heparin or EDTA, may be used. Serum separator tubes should be avoided.
- Samples are stable for 24 hrs at 2°C to 8°C and 1-2 weeks at -20°C.

Assays:

1. Radio-Immune Assay (RIA):

- RIA has become most popular method of Digoxin analysis because of it is sensitive, precise and easy to perform.
- The sensitivity of most current RIA kits is 0.2 - 0.4 ng/ml of serum.
- The main problem with Digoxin RIA is low specificity. Interference by endogenous Digoxin like immunoreactive substances (DLIS) occurs in patients with renal failure, hepatic failure, in pregnant women in third trimester, and in neonates.
- Various methods have been used to decrease this interference, with the most effective being a solid-phase extraction pretreatment.

2. Enzyme Immune Assay (EIA):

- It is a more recent development than RIA and the precision and sensitivity of EI are similar to those of RIA.

3. Fluorescence Polarization Immunoassay:

- The method is based on the ability of a fluorescence labeled Digoxin tracer to compete with unlabeled serum Digoxin for antibody binding sites.
- This method has excellent reproducibility, with a coefficient of variation of less than 6%.
- Interference with DLIS does persist.

4. Chromatographic Methods:

- However the usual means of detection in

chromatography do not permit analysis of serum concentrations because of the general lack of detectable functional groups on the Digoxin molecule.

- Use of levels for dosage adjustment:

- Because of the linear elimination behavior a given increase in the daily Digoxin dose will produce a proportional increase in the serum concentration at that time during the dosing interval.

- Protein Binding:

Digoxin is only 20-30% bound to serum proteins.

Lidocaine:

- Lidocaine is an antiarrhythmic used as second line therapy for treatment of ventricular tachycardia and fibrillation.
- Also used for management of chronic pain syndromes of neurogenic origin due to its local anesthetic property.

Therapeutic Range:

- 1.5-5.0 µg/ml, with concentration greater than 6.0 µg/ml considered to be toxic.
- Side effects above 3 µg/ml drowsiness, dizziness, euphoria, paresthesia.
- > 6 µg/ml (more serious side effects) Muscle twitching, confusion, agitation and psychosis.
- 8 µg/ml, cardiovascular depression, AV block, hypotension, seizures and coma.

Sample Timing:

- The half-life of lidocaine ranges from 1.5 hrs. To as long as 5 hrs. in patient with a liver disease. Thus steady-state is attained after 18-24 hrs. even if a loading dose is administered.
- Because lidocaine is administered as a continuous infusion, there are no fluctuations in levels, and blood for lidocaine serum con determinations can be drawn anytime at steady state.

• Specimens Collection Methods:

- Blood collected in serum separator tubes and tubes containing rubber stoppers.
- Plasma is also acceptable as specimen if heparin or EDTA is used as the anticoagulants.
- Lidocaine is stable in serum or plasma stored 24 hours at 2°C to 8°C or 1-2 weeks at -20°C.

Assays:

- Immunoassays for determination of lidocaine are commercially available and show little cross-reactivity with lidocaine metabolites.
- They do not permit separate determination of the primary active metabolite, mono ethyl glycin-exylidide (MEGX), which has 80-90% of the activity of lidocaine.
- Chromatographic methods (HPLC and GLC) are preferred if monitoring of the active metabolite is deemed necessary.

Use of levels for dose adjustment:

- Adjustments of lidocaine infusion rate should result in a proportional increase in the serum concentration.

Protein Binding:

- The unbound % of lidocaine is normally 30% but can range from 10-40% due to variations in α-1 acid glycoprotein

Procainamide:

Procainamide is used orally for long term suppression of ventricular arrhythmias and long term prevention of chronic supraventricular tachycardia, atrial fibrillation.

- It may also be used intravenously for life threatening ventricular arrhythmias, among other indications.

Indications for TDM:

- Suspected toxicity
- Anticipated pharmacokinetic alterations caused by drug-drug interactions (including amiodarone, cimetidine, ethanol, ofloxacin, quinidine, ranitidine, trimethoprim)
- Changes in disease state (renal failure, CHF)

Therapeutic Range:

- The therapeutic range 4-8 µg/ml, with levels up to 12µg/ml for additional benefits.
- The therapeutic range of procainamide is complicated by the presence of an active metabolite, N-acetyl procainamide (NAPA). Procainamide is a type I antiarrhythmic, while NAPA is a type III antiarrhythmic.
- Most clinicians consider toxic procainamide level to be above 16µg/ml.
- > 8 µg/ml: Anorexia, nausea, vomiting, diarrhea, weakness, and hypertension.
- >12 µg/ml: heart block, ventricular conduction disturbances, new ventricular arrhythmias, and even cardiac arrest.

□ Sample Timing:

- The half-life of procainamide in adults: 2.5 hours (fast acetylator) and 5 hrs (slow acetylator).
- The half-life of NAPA is longer: 6 hours (normal renal function), and 40 hours (renal impairment)
- Thus steady state of both chemicals is not observed until at least 18hrs in patients with normal renal function or as long as 5 days in renal impairment.

Specimens collection methods:

- Serum or plasma, anti-coagulated with heparin, EDTA or oxalate may be used.
- Serum and plasma are stable for 24 hours at 2°C-8°C, and for 1-2 weeks at -20°C.

□ Assay:

- The most commonly used automated assays

for procainamide and NAPA are FPIA and EMIA.

- HPLC and GLC allow the simultaneous measurement of procainamide and NAPA and are not subject to interferences from hemoglobin, lipids or bilirubin.

- Use of levels for dose adjustment:

- The 20% lower clearance of procainamide at higher dose rates has been attributed to non-linear hepatic clearance.

- Protein binding:

It is only 10-20% bound to serum proteins.

- **Quinidine:**
  - Atrial and ventricular premature contractions
  - Paroxysmal supraventricular tachycardia
  - cardiac arrhythmias (IV)

  } oral

Sample timing:

- The $t_{1/2}$ of quinidine is 4-8 hours in adults and up to 10 hours in patient with liver disease. Steady-State should be attained within 2-3 days and the samples should be drawn within 1 hours of next dose.

- Specimen collection method:
  - Serum or plasma may be used.
  - Plasma should be collected in EDTA treated tubes.
  - Serum Separator should be avoided.
  - Quinidine in serum or plasma is stable for 1-2 weeks at -20°C.

- Assays:

It is most frequently assayed by immune