Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Effects of impaired kidney function on drug pharmacokinetics and pharmacodynamics

Section Leaders:

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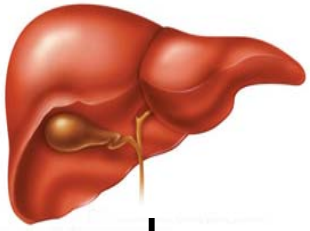
Passage of a Drug Dose Through the Body (Pharmacokinetics)

Oral absorption

(Bioavailability is the proportion of an oral dose reaching systemic system)



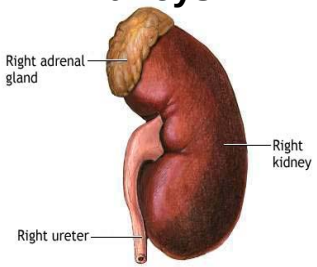
Liver
First-pass effect

Systemic circulation

Bound to proteins
↓ ↑
Free

Parenteral drug administration

Kidneys



Elimination

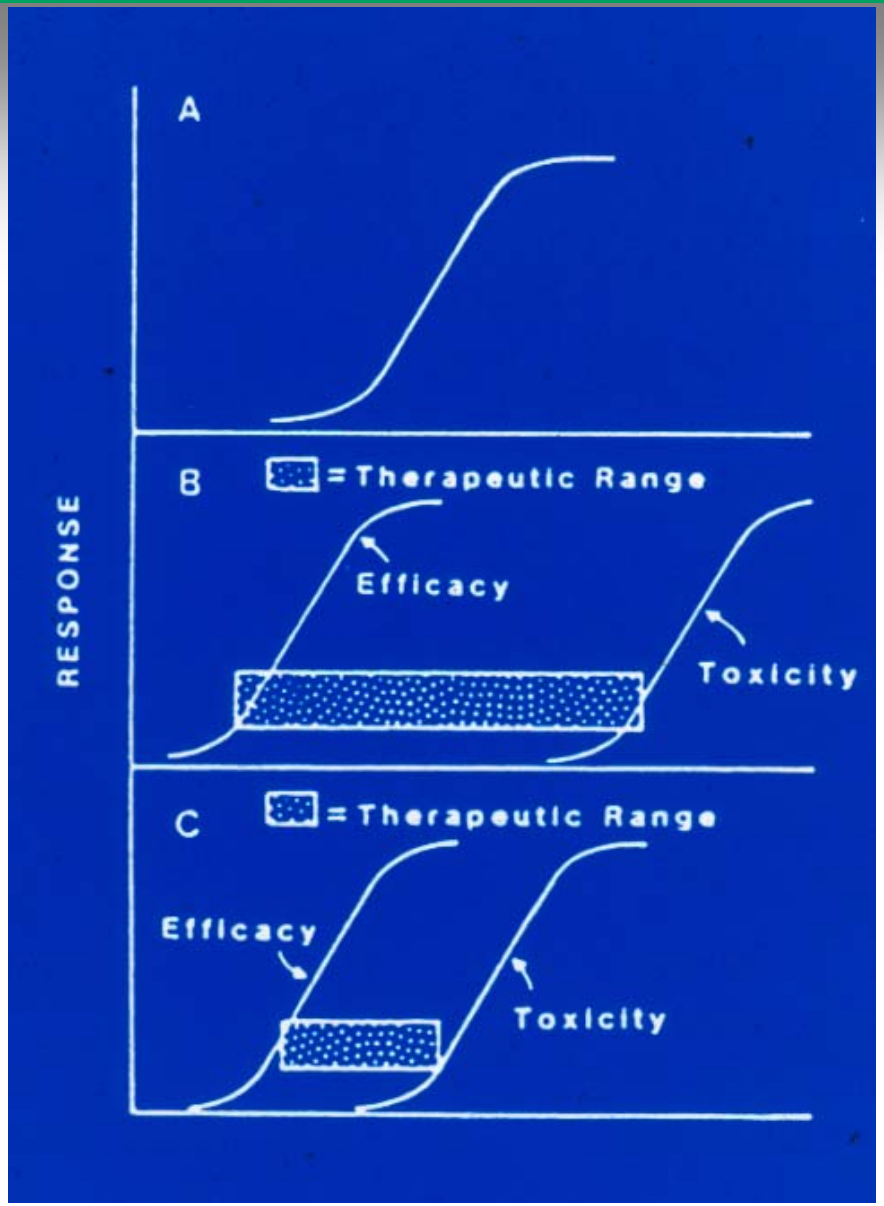
Parent drug

Active/inactive metabolites

Tissue receptor: action

Pharmacodynamics

Kidney Diseas



Kidney Disease: Improving Global Outcomes

Effects of Age and Renal Dysfunction on Pharmacokinetics and Pharmacodynamics

- All processes affected by both variables in complex ways
- Drug elimination primarily affected by ↓ GFR (age +/- CKD)
- Formulae for GFR estimation not validated for drug dosing purposes
- Biologic readouts better than kinetic surrogates ie. blood levels vs. BP, INR, etc.
- Drug interactions multiple and personal

Pharmacokinetic Parameters Affected by Age/GFR

Parameter (abbreviation)	Clinical Application
Bioavailability (F)	Determines the amount of drug reaching the systemic circulation and therefore the amount at the site of action
Volume of Distribution (VD)	Determines the size of a loading dose
Clearance (Cl)	Determines the maintenance dose
Half-life (T1/2)	Determines the amount of time needed to reach steady state serum concentrations or eliminate the drug (four times the T1/2)

Effect of Renal Dysfunction on Drug Usage

- Accumulation of drugs “normally” excreted
- Accumulation of “active” metabolites
- Change in drug distribution - protein binding
- Decrease in renal drug metabolism

Goals of Therapy

- Maintain efficacy
- Avoid accumulation and toxicity

Prescribing for a Patient with Renal Dysfunction

- Ascertain level of renal function (estimated GFR/C_{Cr})
- Establish integrity of liver metabolism
- Establish loading dose
- Maintenance dose - dose reduction vs. interval extension
- Check for drug interactions
- Decide whether blood level monitoring is indicated

Estimated GFR – MDRD Formula

- eGFR (mL/min/1.73 m^2) = 175 [Serum Creatinine (umol/L) x 0.0113]$^{-1.154}$ x age (years)$^{-0.203}$
- If female, multiply the result by 0.742
- If African American, multiply the result by 1.21
- Not valid for eGFR > 60
- Not valid for very fat, very thin, paraplegics, elderly

Cockroft-Gault Equation

$$\frac{140 - \text{age} \times (\text{lean body weight}) \times 0.85 \text{ (if female)}}{72 \times \text{serum creatinine}}$$

References Regarding GFR Estimation for Drug Dosing

- Wango et al., Comparison of MDRD and CG equations for antimicrobial dose adjustments. *Ann Pharmacother* 2006, 40:1248.
- Stevens et al., Comparison of drug dosing recommendations based on measured GFR and estimating equations. *Am J Kidney Dis* 2009, 54:33.

The Loading Dose

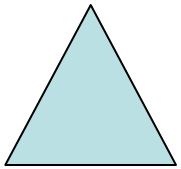
Loading dose = desired Cp_{SS} x V_D x patient's weight

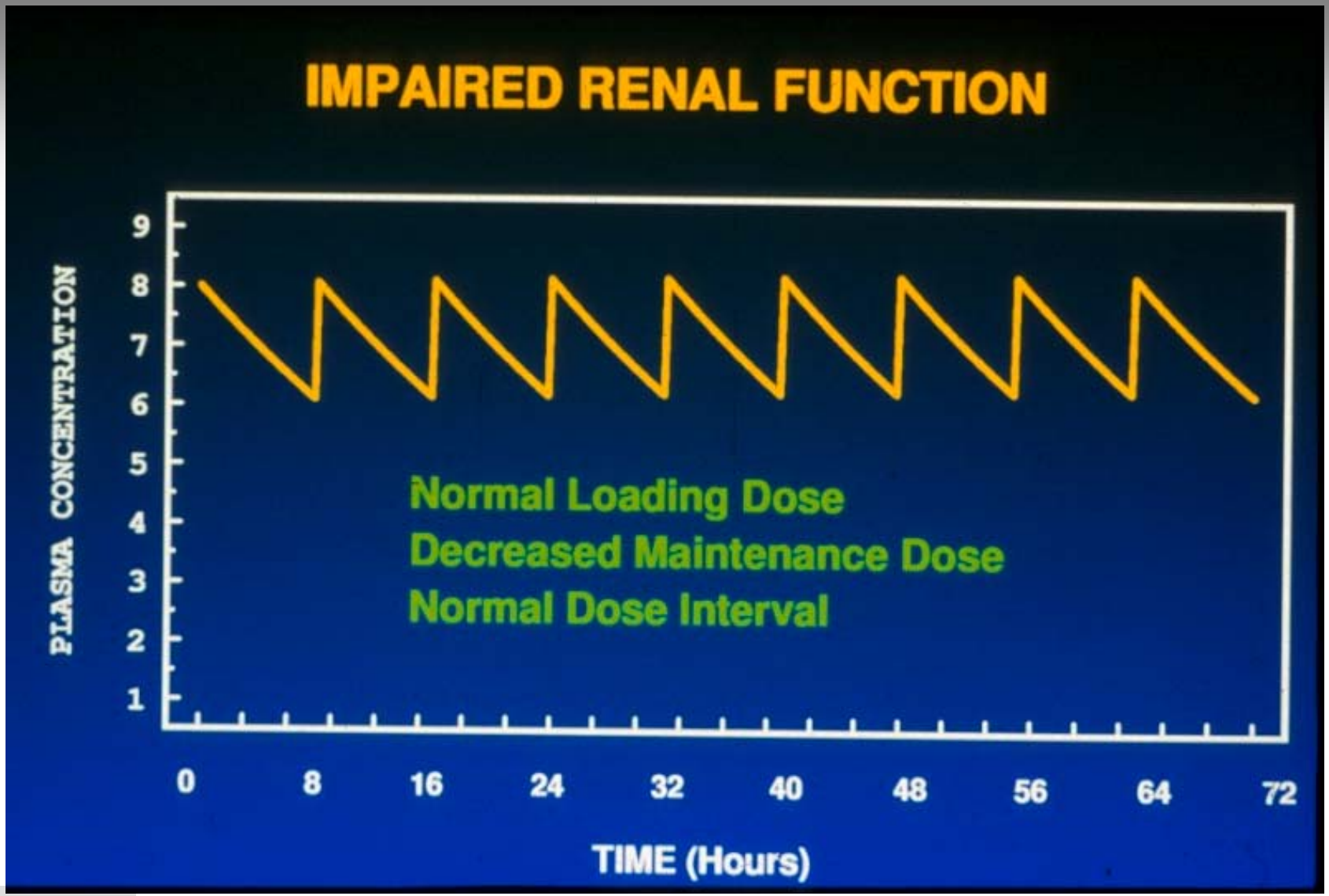
Cp_{SS} = plasma concentration of the drug desired at steady state

V_D = volume of distribution

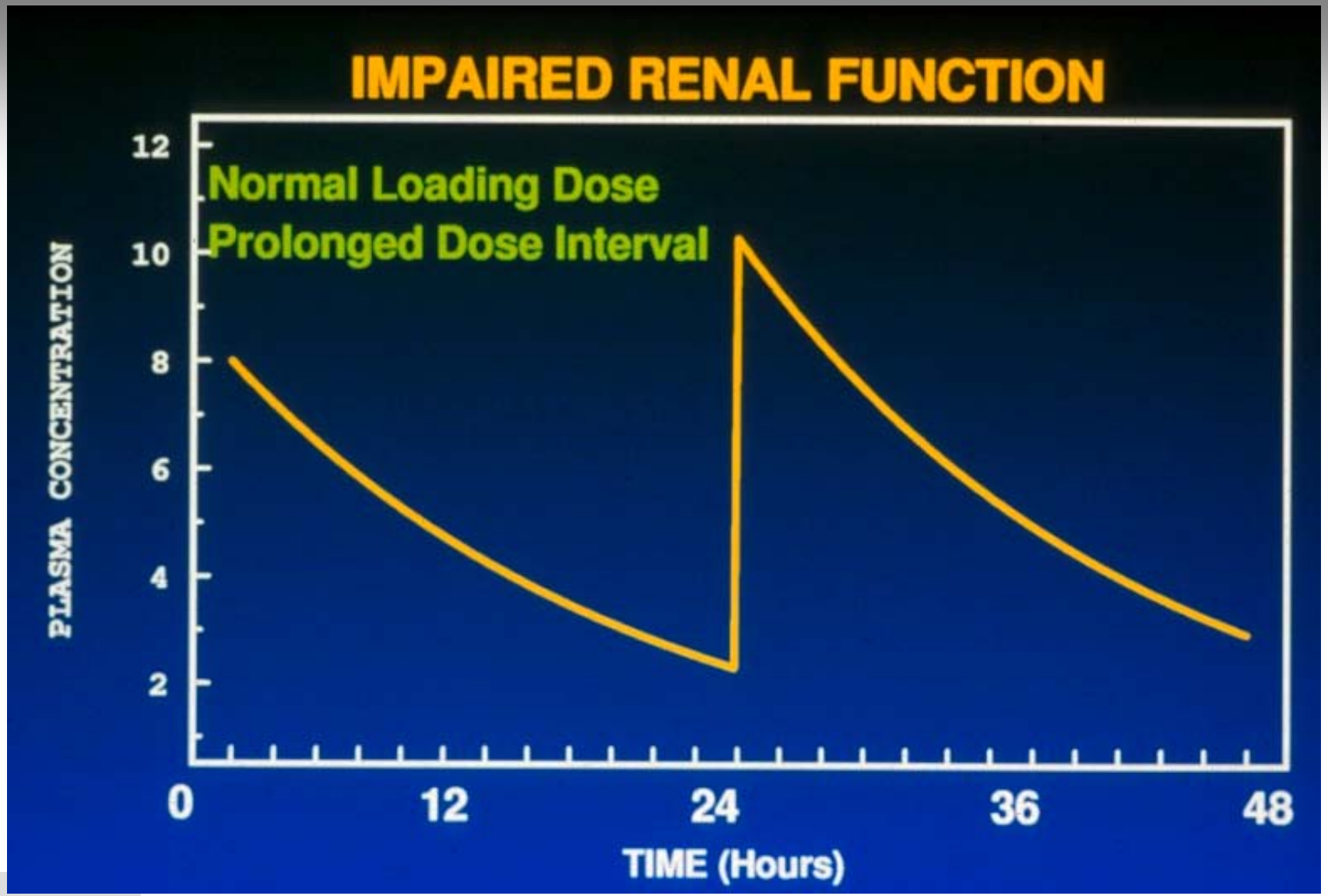
Methods of Drug Dose Adjustment in Patients with CKD

Constant Dose Varying Interval	Constant Interval Varying Dose





Kidney Disease: Improving Global Outcomes


IMPAIRED RENAL FUNCTION
Normal Loading Dose
Prolonged Dose Interval
PLASMA CONCENTRATION
12
10
8
6
4
2
0
12
24
36
48
TIME (Hours)

Examples of Renally Excreted Metabolites in CKD

Active

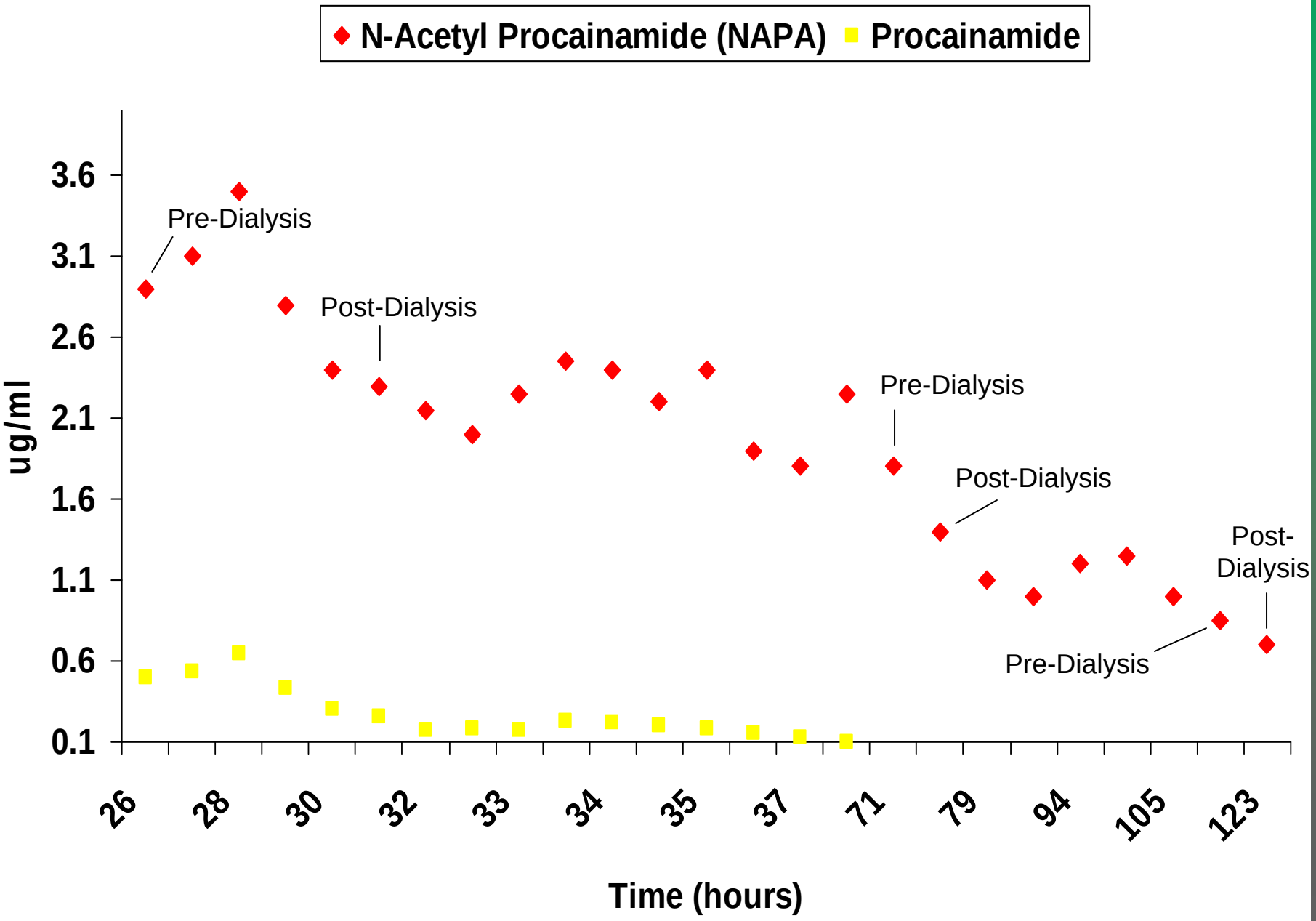
Diazepam → Desmethyldiazepam

Toxic

Meperidine → Normeperidine

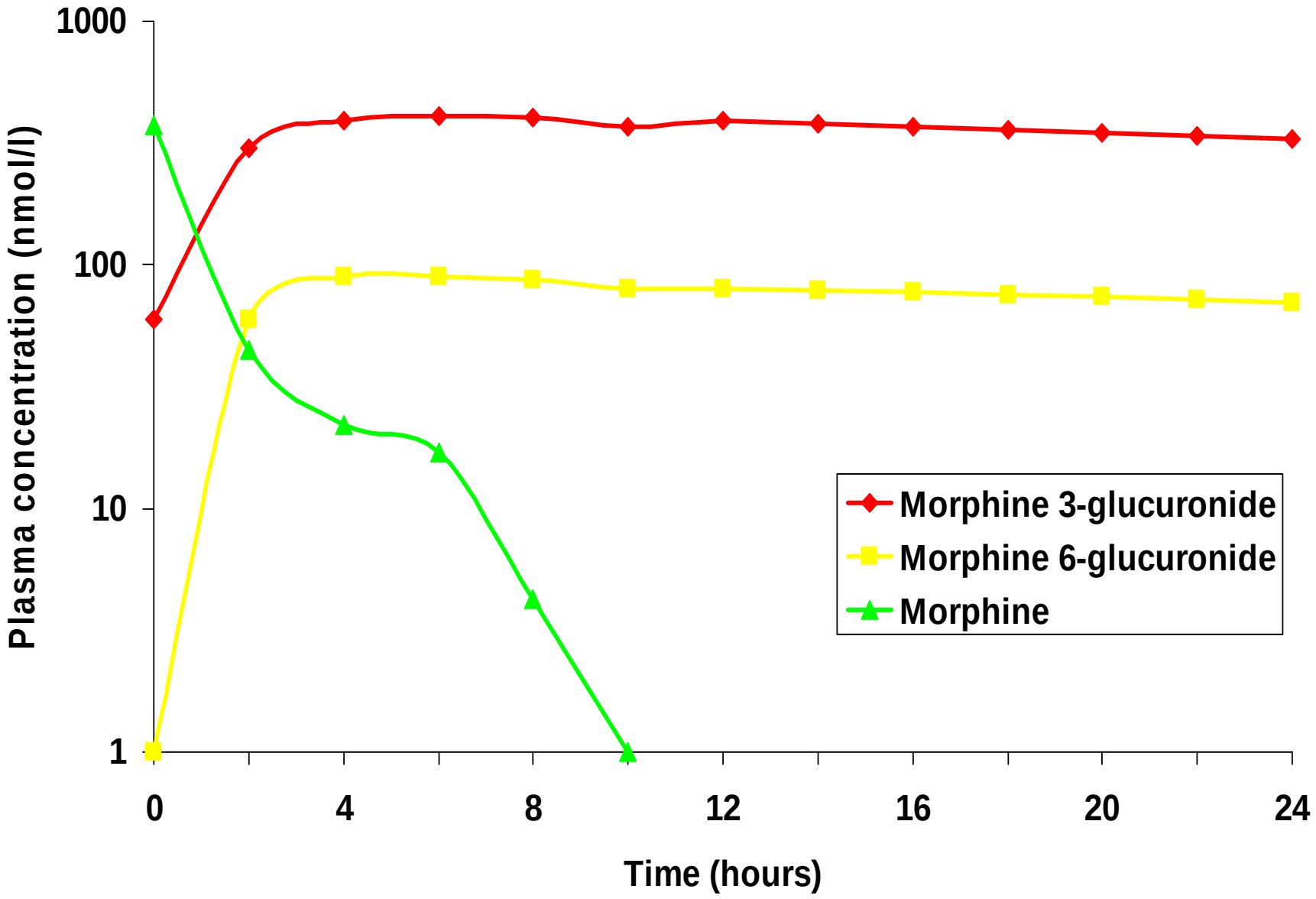
Additive

Procainamide → NAPA


N-Acetyl Procainamide (NAPA)
Procainamide
ug/ml
3.6
3.1
2.6
2.1
1.6
1.1
0.6
0.1
Pre-Dialysis
Post-Dialysis
Pre-Dialysis
Post-Dialysis
Pre-Dialysis
Post-Dialysis
26
28
30
32
33
34
35
37
71
79
94
105
123
Time (hours)

Specific Drugs with Renal Dysfunction

- Narcotics
- Antibiotics/Antivirals
- LMW Heparins


1000
100
10
1
Plasma concentration (nmol/l)
0
4
8
12
16
20
24
Time (hours)
Morphine 3-glucuronide
Morphine 6-glucuronide
Morphine

Antibiotics to be Adjusted*

- Cephalosporins Imipenems: Syndromes of neurotoxicity described
- Penicillins: Neurotoxicity/seizures
- Acyclovir/Ganciclovir: Leukopenia, neurotoxicity, renal dysfunction
- Minimal Adjustments: Fluoroquinolones, sulfonamides

Low Molecular Weight Heparin (LMWH) in CKD)

Lim et al. *Annals of Int Med* 2006

- LMWH excreted by kidneys
- eGFR < 30 mL/min lengthens $t^{1/2}$ and increases anticoagulant anti-X_a
- Increased risk of major bleeding not easily reversed
- Need for downward dose adjustment

Rules of Thumb for Changing Maintenance Drug Dosage

- Available options:
  - Decrease the dose, keeping the interval constant
  - Increase the dose interval, keeping the dose constant
- Decide the appropriate dosage regimen for the patient as if renal function were normal
- Determine the fraction of drug and active metabolite that is excreted unchanged by the kidneys
- Calculate the dosage adjustment factor. This factor is the ratio of the half-life of the drug in the patient to the half-life of the drug in the normal person

Rules of Thumb for Changing Maintenance Drug Dosage (cont'd)

- Use the dosage adjustment factor in one of the following ways after considering which is most appropriate for the individual drug:
  - Divide the dose you determined for normal renal function by the dosage adjustment factor and continue with the same dosage interval
  - Continue with the same dose but multiply the dosage interval you determined for normal renal function by the dosage adjustment factor
  - A regimen of combined dose reduction and dose interval prolongation may maintain a more uniform serum concentration

Drug Level Monitoring

Drug toxicity is serious and occurs at levels close to “therapeutic”

Therapeutic and biologic end points are not easily defined

To exclude non-compliance or marked interindividual differences

Problems with Current Data

- Kinetic studies performed in few stable CKD patients without comorbidities, acute illness
- Liver and non-renal metabolism varies (age, genetics, illness, other drugs)
- No “cookbook” to make rational individual patient decisions; **Requires Wisdom**

Conclusions

- Prescribing in CKD is an art not science at this point
- No substitute for knowing the drug pharmacology and the individual patient
- Individualize. “Go Low/Go Slow” is a good general rule
- Review med lists including OTC “supplements” at each visit
- Watch for nephrotoxins

Breakout Group 1: Discussion Questions/Objectives

Breakout Group 1: Clinical Recommendations

Breakout Group 1: Research & Regulatory Recommendations