Chapter-V
Drug use in renal and hepatic disorders.

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Estimating renal function

An accurate estimation of renal function, or glomerular filtration rate (GFR), requires sophisticated techniques that are unsuitable for routine or repeated use. In practice, the serum creatinine concentration is used for day-to-day assessment of renal function. It has limitations, but it remains a robust and practical parameter for most clinical situations

Serum creatinine

The serum creatinine concentration has important limitations when used for estimating renal function.

1. There is an inverse relationship between serum creatinine and renal function. A doubling of serum creatinine represents a halving of GFR. A person's serum creatinine can rise from 60 to 120 micromol/L and so still be in the normal range (typically 50 to 120 micromol/L), yet the renal function has deteriorated dramatically.

2. Renal function declines steadily with age in adults, but this is not reflected in the serum creatinine, which remains steady or may only increase slightly with age (in the absence of overt renal disease, where it may rise more obviously). An 80-year-old will have approximately half of the renal function of a 20-year-old, despite both having the same serum creatinine concentration.

Serum creatinine

3. Renal function has an approximately linear relationship with lean body mass. In the presence of the same serum creatinine, a 120 kg person will have twice the renal function of a 60 kg person because they have bigger kidneys.
4. Women have a lower muscle mass than men of equivalent weight and age. A woman's serum creatinine represents approximately 0.85 of the renal function of a man with the same serum creatinine.

These limitations are particularly relevant and must be addressed when attempting to measure renal function for the purpose of calculating drug doses.

Creatinine clearance

The serum creatinine concentration represents a balance between its production in the body (from muscle) and its excretion by the kidneys. From this can be derived an estimation of the creatinine clearance by the kidneys, in millilitres per minute (mL/min) or millilitres per second (mL/sec). This is the notional volume of serum that is cleared of creatinine in those times. The creatinine clearance is the 'poor man's' equivalent of the formal measurements of GFR, but for most clinical purposes is an adequate measurement of renal function.

Creatinine clearance

Manufacturers' renal dosing recommendations for medications are based on Cockcroft-Gault estimates of renal function, so this formula is also recommended when estimating creatinine clearance for the purpose of calculating drug doses that vary according to renal function.

Some important limitations of the Cockcroft-Gault estimation of renal function. It is:
1. not validated in some populations
2. unreliable in extremes of body size (that is, in severe malnutrition or obesity)
3. imprecise and unreliable for rapidly changing renal function (for example intensive care, acute renal failure).

Changes in drug response in renal failure:

1. Brain more sensitive to depressant action of drugs- blood brain barrier is less effective
2. Control of body fluid volume affected. If patient hypovolemic due to diuretics, body becomes very sensitive to action of antihypertensives
3. Impairment of coagulation- more sensitive to anti-coagulants---GI bleed
4. Drugs causing Na^+ retention---NSAIDs—fluid overload---CHF
5. Renal failure—hyperkalemia---ACEI, ARBs.
6. Renal failure---acidosis- altered response to drugs, especially weak acids
7. $\Downarrow$ Cholinesterase activity $\Rightarrow$ more sensitive to AChase drugs—e.G. neostigmine

General principles of prescribing in renal failure:

GOOD KNOWLEDGE OF PHARMACOKINETICS OF THE DRUGS USED IS NECESSARY!

- Use drugs only if a definite indication is present
- Choose a drug with no/minimal nephrotoxicity
- Use recommended regimen given. If no data, use your COMMONSENSE!
- Use TDM to adjust doses
- Avoid prolonged courses of potentially toxic drugs
- Monitor patient for clinical effectiveness & toxicity

Modification of dosage regimen:

- Look at the drug's renal & non renal elimination (%)
- How toxic the drug is

Two approaches:

Standard dose -----Extended intervals

Reduced dose----usual intervals.

LOADING DOSE REMAINS THE SAME!

For many drugs, an unchanged loading dose followed by half the usual adult maintenance dose is all that is done!

For more toxic drugs use dosage regimen based on GFR.

Subsequent dosage based on:

- Clinical response
- Signs of toxicity
- Plasma concentration.

Modification of dosage regimen:

If antibiotic given in usual doses but at extended intervals----there may be considerable periods of sub-inhibitory Concentrations.

More frequent doses---toxicity!

Measure plasma concentrations frequently. Risk versus benefit

Use of tables--- given as appendices in major text books.

Following data is given:

1. Elimination $t_{1/2}$---both normal & in renal failure
2. Unchanged excretion (%)
3. Normal extra renal excretion
4. Normal dose interval (hours)
5. Dose adjustment for renal failure based on Creatinine clearance (ml/min): >50, 10-50, <10.

Limitations of tables:

1. Status of renal function should be determined not only before, but also the entire period of treatment
2. These dosage guidelines do not necessarily apply to elderly patients.
3. Many aspects of individual patients influence drug response in uremia
4. Monitor plasma concentration, especially for drugs with a low therapeutic index.
5. Monitor patients for unexpected drug toxicity.

Nomogram method:

Based on:

Linear relationship between total plasma drug clearance and GFR as determined by creatinine clearance.

Normal renal function is defined by creatinine clearance = 100 ml/min =6 l/hr.
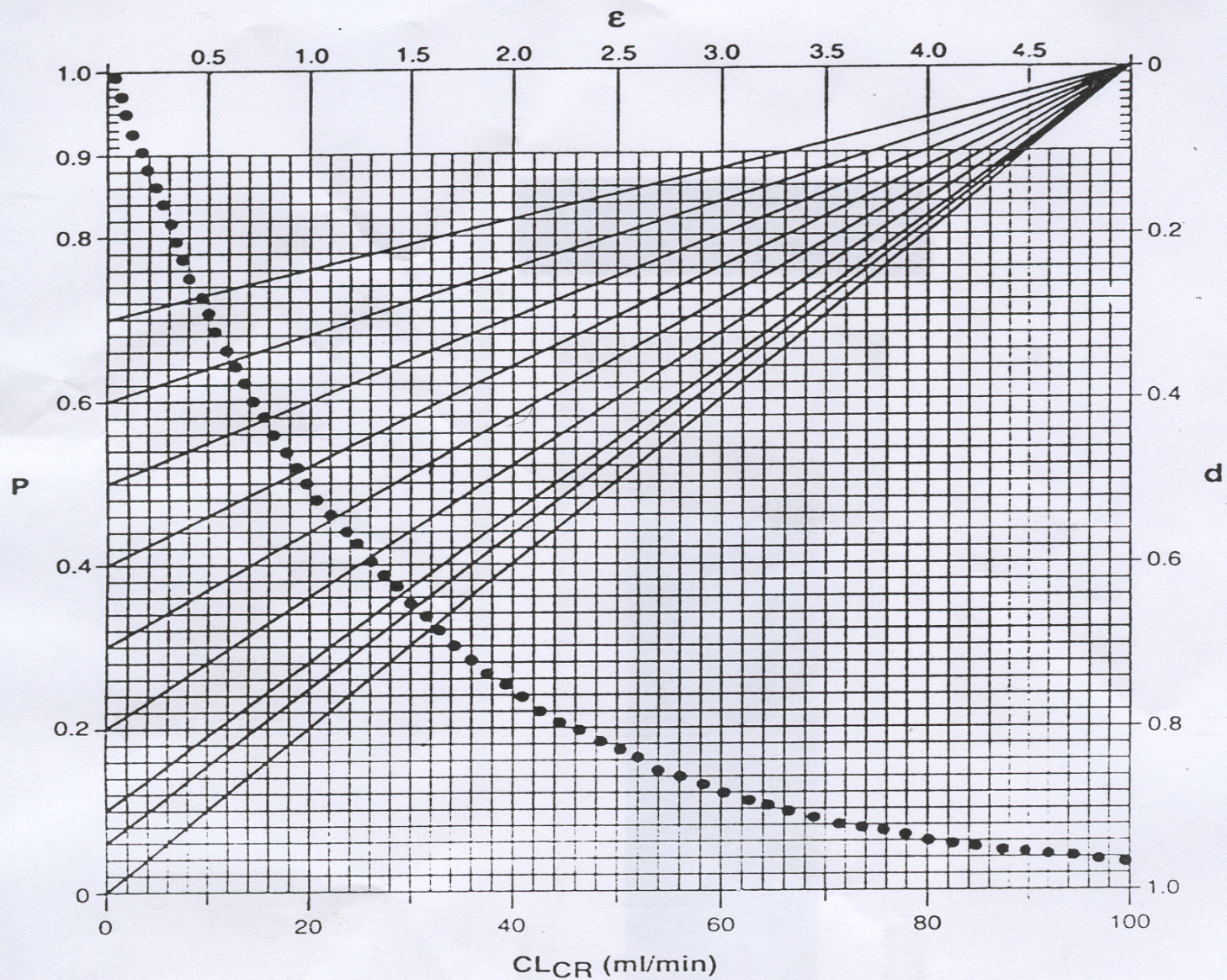
Nomogram for the graphic determination of the individual drug clearance fraction of a drug in a patient with renal failure. P (left e) from the endogenous creatinine clearance, CL_{CR} (lower abscissa), and of the decay fraction, d (right ordinate) from the relative e interval, $\varepsilon = T/t_{1/2}$ (upper abscissa). Use of the nomogram is explained in the text (after Spring[2] by permission of the author tor). For drug P_c [f(sin)] values, see appendix A.

Graphic estimation:

Individual drug clearance fraction (P), which describes the total clearance of the drug in the patient with renal function as a fraction of its normal clearance is determined in the following way by means of the nomogram:

Value of normal non- renal drug clearance fraction $f_{NR(n)}$ (P_o), obtained from appendix in a text book, is plotted on the left ordinate of the nomogram & connected with its right upper corner by a straight line.

The point of intersection between the patient's endogenous creatinine clearance Cl_{CR} (lower abscissa) & the estimating line indicates the left ordinate the individual clearance fraction (P) in the patient.

The ($t_{1/2}'$) is calculated from normal $t_{1/2}$ as:

$$t_{1/2}' \quad = \quad t_{1/2} / P$$

Dosage rules:

Rule 1 :   Rule 2 :

$D_*' \quad = \quad D^*$ $D_*' \quad = \quad D^*$
$D' \quad = \quad D.P$ $D' \quad = \quad D$
$T' \quad = \quad T$ $T' \quad = \quad T/P$

Where $D^* = $ Loading dose D' is maintenance dose & $T = t_{1/2}$.

LOADING DOSE IS SAME IN BOTH RULES.

Rule1 :

Decrease the maintenance dose, dosing Interval unchanged

Rule 2 :
Normal maintenance dose, dosing interval unchanged.

Cockcroft & Gault equation:

$$CL_{CR} \text{ (ml/min)} = \frac{(140\text{-age}) \times \text{Bodyweight (Kg)}}{72 \times C_{CR} \text{ mg/dL.}}$$

In females multiply the result by 0.85

Example:- Administration of cimetidine in a 60 – yr old female patient with a bleeding gastric ulcer. Body weight = 70 kg., plasma creatinine C_{CR} = 2 mg/dl

$$Cl_{CR} = \frac{(140 – 60) \times 70 \times 0.85}{72 \times 7}$$

$$Cl_{CR} = 33 \text{ ml/min}$$

Non-renal clearance fraction of cimetidine = 0.25 (P_o). The value P_o = 0.25 is plotted on the left ordinate, connected with the upper ® corner of the monogram by a straight line. The point of intersection between CL_{CR} = 33 (lower abscissa) with this estimating line results in the individual drug clearance fraction P = 0.5 at the left ordinate.

Assume $D^* = 200mg$ $D = 200mg$ & $T = 4$ as the normal dosage regimen of cimetidine.

Rule 1

$D'_* = D^* = 200mg$

$D' = D.P = 200 \times 0.5$

$\quad = 100mg$

$T' = T = 4$ hours

Rule 2

$D'_* = D^* = 200mg$

$D' = D = 200mg$

$T' = T/P = 4/0.5$

$T' = 8$ hours

So, give 100 mg cimetidine every 4 hourly or 200 mg every eight hourly

Limitations of nomogram:

1. Serum Creatinine should never be used as an estimating parameter in patients with acute renal failure or changing kidney function.
2. Does not obviate need for therapeutic drug monitoring (TDM).
3. Carefully observe patients for unexpected drug toxicity.

During usage in hepatic diseases

Drug distribution: ↓ plasma albumin & ↓ bilirubin

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Decreased plasma protein binding

Drug Elimination:- Depends on type & stage of liver disease.

- There is ↓ portal venous perfusion to a liver of ↓ cell mass.
- Intrahepatic shunts with in the liver

Drug Elimination:

- Abnormal sinusoidal membrane – loss of fenestration & ⇓ permeability
- Extra hepatic shunts.
- Of all Liver function tests → serum albumin concentration & vitamin K corrected prothrombin time provide the best estimates of hepatic metabolic capacity.
- Decreased intrinsic clearance of many drugs.
- Drugs with high hepatic clearance show ⇑ bioavailability ⇒Propranolol, pethidine, pentazocine, labetalol, clomethiazole.

Drug Elimination:

- Decreased hepatic metabolism
- Decreased hepatic clearance of many drugs.
- Glucuronidation is relatively preserved in patients with liver disease.
- *No single test/ Model/ Marker compound as predictors of hepatic functional reserve!*
- Adjusting dosage is more difficult than in renal disease.

Use of tables:- As appendix in Text books.

5 major Pharmacokinetic variables:

1. Clearance
2. Volume of distribution (V_D)
3. Elimination t $_{1/2}$
4. % unbound drug
5. Bio availability

Rate of drug admin = Cl x C_{SS}

Cl = clearance

Css = concentration at steady state (~ 5 $t_{1/2}$)

Eg:- Css of theophylline is 10mg / L & Cl =3L / h.

Dosage rate   =   10mg x 3 L   =   30mg/h

or 180 mg every 6 hourly.

V_D: of water soluble drugs with small V_D will have significant ↑↑ in their V_D in patients. With ascites. eg:- aminoglyicosides

Altered Pharmacokinetics:

Impaired intrinsic hepatic eliminating capacity due to lack of or impaired function of hepatocytes

Impaired biliary elimination due to biliary obstruction or transpost abnormalities.

Impaired hepatic blood flow due to surgical shunting, collateral circulation or poor hepatic perfusion with cirrhosis & portal hypertension

- Altered V_D due to differences in body composition with $\uparrow$ ECF (ascites, edema) & $\downarrow\downarrow$ muscle mass.

- $\downarrow\downarrow$ plasma protein binding due to impaired albumin production or drug displacement from accumulated substance normally cleared by the liver

- $\uparrow$ Bio avail through $\downarrow\downarrow$ first pass metabolism

- $\downarrow\downarrow$ Bioavailability due to malabsorption of fats in cholestatic liver disease.

Limitation of tables:

Data is generated in small number of patients mostly with alcoholic cirrhosis.

Other diseases not well studied.

For same degree of liver impairment some patients show impaired ability to clear the drug & other have clearance comparable to healthy controls.

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- Ability to metabolize one drug may not be predictive of their ability to metabolize another agent.
- One enzyme system may be significantly impaired another may remain intact.
- <u>Pharmacodynamics:</u> Best eg: is ↑↑cerebral sensitivity of analgesics antianxiety & hypnosedative drugs in patients with liver disease especially hepatic encephalopathy.
- Avoidance of these agents is strongly advised