Drugs and the Kidney

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Definition:
Toxic nephropathy may be defined as the adverse functional and/or structural changes in the kidney caused by chemical or biological product that is inhaled, ingested, injected, absorbed, or yields metabolites with an identifiable toxic effect on the kidney.

Drug Induced Renal Disease:
Two mechanisms are involved:
1. Drug toxicity.
2. Drug allergy.

Drug Toxicity:
Recognizes that all drugs are potential poisons. It is more frequent in patients with reduced renal function when drug excretion is impaired, it is dose related and can be predicted.

Drug Allergy (Drug Hypersensitivity)
Refers to those adverse effects which have or are inferred to have an immunologic basis. These are not predictable. Reaction is not dose dependent. It occurs after 8 to 36 days period of sensitization.

Nephrotoxicity of Drugs:
A. Drug-induced direct nephrotoxicity accounted for 25% of all cases of acute renal failure. Aminoglycosides are the major offenders. Drug-induced nephrotoxicity is usually nonoliguric (75%) and associated with low mortality (12%).

B. Hypersensitivity nephrotoxicity occurs predominantly following therapy with methicillin and other penicillins. Other drugs implicated include rifampicin, sulfonamides and furosemide. Most patients have fever, 50% have a drug rash and eosinophilia is common. Oligouria and need for dialysis is present in 50% of cases. Frequently, evidence of proximal and distal tubular dysfunction is present (glycosuria, RTA), eosinophilic casts in urine are diagnostic. Corticosteroids may shorten the course of renal failure.

Clinical Patterns of Renal Damage Induced by Nephrotoxins:
1. Acute renal failure.
2. Chronic renal failure.
3. Nephrotic syndrome.
4. Generalized or specific tubular disorders.

Drug Induced Renal Disease:
Drug induced ARF is relatively common. In a prospective one year study of all cases of ARF at one institution, it was found that drugs/toxins accounted for 20% of all cases of ARF.

1. Acute Renal Failure:
Different clinical pattern:
(A) Direct tubular toxicity or A.T.N.
(B) Acute interstitial nephritis.
(C) Renovascular lesions.
(D) Acute glomerulonephritis.
(E) Obstruction.

A. Direct Tubular Toxicity or A.T.N.
a. Nephrotoxins Causing A.T.N.
Antimicrobial Agents: Aminoglycosides (gentamycin, kanamycin, tobramycin, etc.) Cephaloridin (other cephalosporins) Polymyxin, Colistin. Amphotericin, Tetracyclines.
Heavy Metals: Mercury, bismuth, uranium, arsenic, silver, iron, antimony, copper sulphate, gold.
Solvent & Glycols: CC14, trichloroethylene, glycol.
Pigments: Haemoglobin and myoglobin.

b. Toxic Causes of Haemoglobinuric Tubular Necrosis:
Drugs: Quinine sulphate, quinidine sulphate, hydrazine, sulfonamides.
c. A.R.F. Secondary to Vascular Disease:
Necrotizing angitis and periarteritis nodosa like picture with I.V. amphetamine.

B. Acute Interstitial Nephritis

FREQUENT
Methicillin
Penicillin
Ampicillin
Rifampicin
Glafenin
Tetracycline
Sulfonamides
Thiazide
Cotrimoxazole
Phenindione
Phenytoin

RARE
Oxacillin
Nafcillin
Carbenicillin
Cephalothin
PAS Acid
Furosemide
Phenybutazone
Aminophenazone
Gold and bismuth salts
Azathioprine
Allopurinol
Phenobarbital

C. Acute Glomerulonephritis:
(i) Penicillins
(ii) I.V. drug abuse, heroin nephropathy.
(iii) Drug induced SLE.

D. Obstruction:

Intrarenal:
Uric acid loads induced by chemotherapy of neoplasms or uricosuric drugs.
(ii) Sulphonamides.
(iii) Oxalate precipitation from drugs (Ethylene glycol, Methoxyflurane) or disorders (small bowel resection).
(iv) Contrast media.
(v) Methotrexate.

Extrarenal:
Due to papillary necrosis from analgesic abuse, due to clots from anticoagulants. Retroperitoneal fibrosis from methysgide.

2. Chronic Renal Failure:
It is known that after drug induced acute kidney injury a small number of patients do not recover and several studies have documented persistent functional and structural defects. Chronic drug use or abuse can cause insidious renal damage and failure. At present syndrome of chronic renal insufficiency is primarily associated with the chronic and excessive consumption of analgesics including salicylates, phenacetin and their metabolites.

3. Nephrotic Syndrome:
Puromycin (experimental prototype), Trimethadione, Ethadione, Paradione Mercury, Bismuth, Gold, EDTA, Penicillamine, Tolbutamide, Probencid, Perchlorate, Snake Venom, Heroin Addiction Allergens in envroment, Bee sting, Poison IVY, Capoten (Captopril).

4. Generalized or Specific Tubular Disorders:

a. Hypokalemic Alkalosis:
Carbenicillin.
Penicillin.
Liquorice Ingestion.

b. Sodium Retention:
Indomethacin
Phenybutazone.

c. Fanconi Syndrome:
Clinical Feature
Aminoaciduria, Glycosuria, Proximal bicarbonate wasting and Renal tubular acidosis' Hypouricemia, phosphaturia.

Symptoms:
Often weakness, polyuria secondary to hypokalemia.

Causes:
Heavy metals (lead, mercury, bismuth, cadmium, streptozocin, outdated tetracycline).

d. Impaired Concentrating Ability:
Polyuria, nocturia, polydipsia and dehydration may be caused by Lithium, demeclocycline, fluoride, methoxylflurane.

e. Impaired Free Water Clearance:
Cyclophosphamide
Vincristine
Chlorprophamid
Carbamazepine
Clofibrate
Amitryptylene
Isoproterenol

Drug Therapy in Patients with Renal Failure:
Since Renal function can affect drug disposition in so many different ways, a physician must be aware of these potential mechanisms to optimally call upon his clinical skills and laboratory to the best care for his patients. Basic determinants of drug accumulation and thus action, include absorption, distribution in the body fluid spaces, metabolism and excretion.

Drug Absorption:
a. Drugs are absorbed more slowly from I.M. sites in patients with renal disease and oedema.

b. The G.I. manifestations of advanced renal failure i.e. nausea, vomiting, diarrhea and G.I. oedema result in retardation of drug absorption.

c. Certain drugs, particularly the nonsteroids anti-inflammatory agents may add to uremic, G.I. symptoms by local irritative effects.

d. The increased salivary urea of uremic patients undergoes conversion by gastric ureases to ammonia and acts to buffer gastric HCL and raise pH. Thus drugs best absorbed in an acidic medium may have impaired absorption in uremic in renal failure.

e. Decreased calcium absorption in uremic patients is there because of deficient I-hydroxylation of 25-OH Vit-D 3.

f. Bioavailability of propranolol is increased in patients with renal disease due to decreased pre-systemic elimination (first pass metabolism).

Distribution depends upon:

A. Systemic pH. which could be acidic due to uremia or alkalotic due to potassium depletion and this intum would influence ionization or non combination of drugs.

B. Protein binding which would effect the free drug level. In uremia, there is hypoalbumenemia and acidosis alongwith decreased protein binding. Examples phenytoin, valporic acid, salicylates, thiopental, diazoxide, commurins.

Elimination of drugs is by two mechanisms:—

(a) by metabolism. 
(b) by excretion.

Kidney does play signifacant role. Insuline is mainly metabolished by the kidney so reduce the dose of insuline in diabetic patients with renal insufficiency. 

Metabolism of drugs predominantly occurs in the liver and metabolites of some drugs may be pharmologically active and depend upon the kidney for elimination e.g. Procainamide-N. acetyle procainamide, pethidine-nor pethidine (Table -4). Some oral sulphanyl urea compounds are converted into active metabolites of the parent compound. Serum determination of the metabolites is not yet fully developed for clinical use.

Kidney is the most important organ of excretion. Filtration; active transport; metabolism; passive transport are all modes of elimination. Only free drug is filtered. Displacement of highly bound drugs from serum proteins increases the amount of free drug eliminated in the urine. e.g. Phenytin; valporic acid. When integrity of glomerulus as a sieve is disrupted drugs bound to albumen are carried with the protein in the urine (e.g. clofibrate; phenytin) enhancing their excretion. Number of functioning nephrons also modify drug excretion. The excretion of aminoglycosides and digoxin is reduced in decreased creatinine clearance. Renal tubules can both actively secrete and reabsorb a variety of substrates. Active secretion of drugs by the kidney is usually considered in terms of compounds which are acidic and basic. The different compounds in the table 1 can compete with each other for secretion. This competition is important clinically. Organic acid diuretics i.e. furosemide; ethacrynic acid; and thiazides reach their site of action by secretion into the lumen. Accumulated organic acids in uremia block the access of these diuretics to their active sites — so large doses of these diuretics are administered to attain sufficient amount in the tubular lumen to cause diurersis. Organic bases transport of which is clinically important are shown in Table 2. Compounds, with clinically important urine pH dependent elimination are shown in Table 3.

<table>
<thead>
<tr>
<th>TABLE – 1</th>
<th>Organic Acids with a Clinically Important Component of Active Transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para-aminohippurate</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>“Loop” diuretics</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Nonsteroidal anti-inflammatory agents</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Probenecid</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Sulphonamides</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>Thiazide diuretics</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>TABLE – 2</th>
<th>Organic Bases with a Clinically Important Component of Active Transport</th>
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</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Mecamylamine</td>
</tr>
<tr>
<td>Mepacrine (quinacrine)</td>
<td>N-Methylnicotinamide</td>
</tr>
<tr>
<td>Procaainamide</td>
<td>Pseudoephedrine</td>
</tr>
<tr>
<td>Tetraethylammine</td>
<td></td>
</tr>
</tbody>
</table>
Transport of clinically important drugs which are not acid or base is a secretory process. Digitoxin and Digoxin elimination can be competed by spironolactone, verapamil and quindine. Patients co-administered these drugs need less cardiac glycosides. The site of Digoxin transport is the distal nephron. Passive transport is modulated by urinary pH and flow rate. Urinary pH favouring the non-ionised molecule facilitates re-absorption.

### TABLE 3
**Compounds with Clinically Important Urine pH-Dependent Elimination.**

<table>
<thead>
<tr>
<th>WEAK ACIDS</th>
<th>WEAK BASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Amphetamine</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Ephedrine</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Mexiletine</td>
</tr>
<tr>
<td>Sulphonamide derivatives</td>
<td>Pseudoephrine</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Phenyclidine</td>
</tr>
<tr>
<td></td>
<td>Quinine</td>
</tr>
<tr>
<td></td>
<td>Tocainide</td>
</tr>
<tr>
<td></td>
<td>Tricyclic antidepressants</td>
</tr>
</tbody>
</table>

### TABLE 4
**Drugs with Active Metabolites of Clinical Importance in Patients with Decreased Renal Function:**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>METABOLITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>N-acetylacebutolol</td>
</tr>
<tr>
<td>Acetoheamidine</td>
<td>Hydroxyhexamide</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Oxyurinol</td>
</tr>
<tr>
<td>Colotaxime</td>
<td>Desacetylatedoxime</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Parachlorophenoxy-isobutric acid.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4-hydroxycyclophosphamide and aldophosphamide</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Uracil arabinoside</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Digoxigenin-mono-digit-oxide &amp; digoxigenin-bis-digitoxide.</td>
</tr>
<tr>
<td>Pethidine (meperidine)</td>
<td>Norpethidine</td>
</tr>
<tr>
<td>Methimazole</td>
<td>3-methyl-2-thiohydantoin</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1-hydroxymetoprolol</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>7-hydroxynalidixic acid</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>3-hydroxypancuronium</td>
</tr>
<tr>
<td>Procainamide</td>
<td>N-acetulproataminde</td>
</tr>
<tr>
<td>Proproxyphene</td>
<td>Norprooxyphene</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>Thiocyanate</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>Toxic acetylated metabolites</td>
</tr>
</tbody>
</table>

### Specific Principles in Drug use in Patients with Renal Failure:

A. Two accepted methods of altering drug schedules for renal failure patients. These are: (1) constant interval, changing dose method (this method is more difficult; it results in stable drug levels) and (2) constant does, changing interval (this method is generally easier; it results in peak and trough blood levels). Neither of these schedules has been documented to be preferable. These schedules can easily be applied to drugs 100% excreted unchanged by the kidney; e.g., if a drug is 100% excreted unchanged by the kidney and kidney function is 50% normal, then the dose could be decreased by 50% maintaining the usual interval or to double the normal dosing interval while the dose is kept constant.

B. For drugs not 100% excreted unchanged by the kidney calculation of dose intervals or dosage becomes more difficult. To calculate the dose interval, the following formula may be used:

\[
Dose \text{ Interval} = Normal \text{ dose interval} \times f(Kf-1) + 1
\]

Where \( f \) = fraction of drug normally excreted unchanged by the kidney and Kf = measure of the patient’s renal function compared with normal renal function; i.e. normal serum creatinine/patients serum creatinine or patients creatinine clearance/normal creatinine clearance.

For example, consider a drug that is normally excreted 60% unchanged by the kidney. This drug is usually administered every 6 hours. Creatinine clearance is 10/min.

\[
Dose \text{ interval} = 6 \text{ hours} \times 0.6 \times (0.1) + 1
\]

\[
6 \times 1.46 = 13 \text{ hours}
\]

In order to change the dose and maintain a constant interval, the following formula can be used:

\[
Dose = Normal \text{ Dose} \times (Kf-1) + 1
\]

### Causes of Adverse Drug Reactions in Patients with Renal Failure:

A. Adverse effects resulting from enhanced pharmacologic effect of drug.
1. Impaired drug metabolism and/or excretion with renal failure leading to high levels of drug.
2. Impaired protein binding of drug with renal failure leading to enhanced drug effect.
3. End organ changes due to uremia leading to enhanced drug effect (e.g. platelet dysfunction of uremia enhanced by salicylates; G.I. bleeding
tendency of uremia enhanced by ulcerogenic
drugs).

B. Adverse effects incidental to pharmacologic effect
of drug.
1. Metabolic loads administered with drugs (magnesi­
um, sodium, potassium, calcium, phosphate, bicarbonate, etc).
2. Direct nephrotoxicity:
a. Aminoglycosides, gold, amphotericin B, pheno­
cetin, methoxyflurane, penicillamine, indo­
methacin, mercurials are all directly neph­
rotoxic.
b. Penicillins, sulfonamides, rifampicin, furose­
mide, azathioprine, allopurinol and thrive­
thadione all may induce nephrotoxicity due
to hypersensitivity.
3. Indirect nephrotoxicity:
a. Diuretic drugs (lithium, tetracyclines, diphe­
nylhydantoin, methoxyflurane).
b. Antidiuretic drugs (chlorpropamide, clofi­
brate, cyclophosphamide, vincristine, car­
bamazepine).
c. Drugs those may induce RTA (lithium, tetra­
cycline, amphotericin B)

C. Effect of renal function on sensitivity to drugs:
The acidemia of uremia may cause resistance to the
pressor effects of catecholamines. This may be true
sensitivity. Electrolyte and acid-base abnormalities
due to renal dysfunction can affect sensitivity to drugs
which affect the C.V.S. Hyperkalemia slows conduc­
tion throughout the heart and increases the similar
effect on conduction of digitalis glycosides, guinidine, proca­
amide, disopyramide, phenothiazines and tri­
cyclic antidepressants. Alkalosis, magnesium or po­
tassium depletion and hypercalcemia increase the
sensitivity to the toxic effect of digitalis.

D. Alterations in target organs in uremia.
Inflammatory and ulcerative changes in gastrointes­
tinal taract provide setting for local irritation of drugs.
Increase susceptibility can be there. Patient may need
larger and more toxic doses of diuretics due to de­
creased glomerular filtration.

DRUG DOSE MODIFICATION

Alteration of drug doses is required for many drugs
in renal failure.

1. No Dose Modification Needed
A. Antimicrobial Agents
   Penicillin (oxacillin, cloxacillin, disocloxacillin, nafacillin)
   Clindamycin
   Chloramphenical
   Erythromycin
   Pyramethamine
   Isoniazid
   Rifampicin
   Ethionamide
B. Arthritis Drugs
   Allopurinol
   Phenylbutazone
   Indomethacin
   Colchicine
   Glucocorticoids
C. Analgesics/Sedatives
   Acetylsalicylic acid.
   Acetominophen
   Propoxyphane
   Pentazocine
   Opiates
   Diazipam
   Chloridiazepoxide
   Chloral hydrate
   Meprobamate
   Diphenhydramine
   Short-acting Barbituates.
D. Drugs Used in Neurology/Psychiatry
   Tricyclics
   Phenothiazines
   Levodopa
   Haloperidal
   Diphenylhydantoin

II. Dose Modification Needed for Slight Reduction in
Creatinine Clearance.
(30–50 ml/min).
A. Antimicrobial Agents
   Aminoglycosides
   Colistimethate
   Vioymycin
   5-Flurocytosine
B. Arthritis Drugs
   Gold
   Probenecid
C. Analgesics/Sedatives
Long-acting barbituates

D. Drugs Used in Psychiatry and Neurology
   Lithium
   Anticholinesterases
   Succinamides

E. Cardiac Drugs
   Digoxin

F. Immunosuppressives
   Methotrexate
   Cyclophosphamide

III. Drugs to be Avoided in Renal Failure

Tetracyclines (except doxycycline)  antianabolic natriuretic and diuretic effect
   increase BUN, rarely nonoliguric ATN. These do not get into urine when creatinine clearance, is decreased.

Nitrofurantoin  may result in disabling neuropathy, do not get into urine with decreased creatinine clearance.

Probenecid  ineffective with creatinine clearance below 50 ml/min, may result in high frequency of untoward reactions.

Drugs to be used with Caution in Renal Failure.

   Antacids  Na+, Ca++, Mg++ load
   Nephrotoxins  enhanced ototoxicity
   Antiplatelet agents  hemorrhagic tendency
   Oral hypoglycemics  hypoglycemia.

   In summary, the kidney can influence the disposition and response to drug in many ways. The clinician must understand not only the pathophysiology of his patient’s disease but also the pharmacology of the drug being used so he can assess clinical end points of efficacy and toxicity as a guide to therapy.

REFERENCES

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