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A Pharmacological Update of Nephrotoxic Drugs

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The pharmacodynamics effects of a drug are of two types-desirable or beneficial effects and undesirable or Adverse Drug Responses (ADRs). The WHO has defined an adverse drug reaction as any response that occurs to a drug which is noxious, unintended and occurs at a dose used in man for prophylaxis, diagnosis or therapy. Toxic effects of a drug are a type of an adverse drug response. They are the result of excessive pharmacological actions of the drug. The central nervous system, cardiovascular system, renal system, liver, skin and blood forming organs are most commonly involved in drug toxicity.

Nephrotoxicity occurs when a drug produces toxic effects on the kidney. It may manifest as alterations in renal hemodynamics, tubular damage and obstruction, glomerular nephropathy or interstitial nephritis. When there is loss of function of large number of nephrons, it results in 'Progressive Renal Failure' characterized by progressive increase in serum creatinine.

Potentially Nephrotoxic Drugs [1-3]

Aminoglycosides (AGs)

All AGs have the potential to produce renal toxicity. Patients receiving AGs for several days develop mild renal impairment that is usually reversible. The toxicity results from accumulation and retention of AGs in the proximal tubular cells.

Mechanism of nephrotoxicity: Renal injury occurs by inhibition of lysosomal enzymes (Sphingomyelinase and Phospholipases) in the proximal tubules of the kidney causing renal phospholipidosis, which is accumulation of non-degraded phospholipids in the lysosomes. The lysosomes eventually rupture causing cell death and acute tubular necrosis develops.

Renal tubular injury by aminoglycosides is reversible upon cessation of treatment. The proximal tubular cells have the capacity to regenerate and the impairment is usually reversible. The most common significant finding is a mild rise in plasma creatinine, although severe acute tubular necrosis occurs rarely.

Dosing of aminoglycosides: Toxicity with AGs occurs due to accumulation of the drug in the kidney. Traditionally, total daily dose of AGs was administered in two to three equal doses. Presently, the guideline is to administer an AG in a single daily dose as it has been found to be less toxic and equally effective on account of the following reasons:

I. Elimination of AGs from the kidney occurs more slowly than plasma and is retarded by a higher plasma concentration.

II. The amount of drug accumulated is more with higher plasma concentrations and a longer period of exposure.

III. Longer the plasma concentration exceeds a relatively safe upper limit higher are the chances of toxicity.

IV. Once daily regimen provides a longer period when concentrations of AGs are below the threshold for toxicity than a multiple dosing regimen.

Amphotericin B

It is a broad-spectrum antifungal drug having the broadest spectrum of activity. It damages fungal cell membrane by interacting with ergosterol (the fungal cell membrane sterol) and introduces pores in the fungal cell membrane. Amphotericin B associated pores in the cell membrane interfere with the transport functions and permeability of the cell and cause loss of intracellular potassium ions and cell death. Some binding of amphotericin B to human membrane sterols does occur which is responsible for the high toxicity of amphotericin B.

Formulations of Amphotericin B: Four formulations of amphotericin B are available to make it suitable for intravenous administration, as it is insoluble in water.

I. C-AMB - Amphotericin B is formulated with bile salt deoxycholate.

II. Amphotericin B colloidal dispersion (ABCD).

It contains equal amounts of amphotericin B and cholesteryl sulphate.

III. Liposomal Amphotericin B (L-AMB).

It has Amphotericin B incorporated within unilamellar liposomal vesicle formulation.

IV. Amphotericin B lipid (ABLC).

It is a complex of two phospholipids.

Nephrotoxicity of AMP-B formulations.

The lipid formulations of amphotericin B decrease its nephrotoxicity.

Except C-AMB, the other three formulations reduce the risk of active kidney disease. Azotemia occurs in 80% of patients who receive C-AMB for deep mycosis. ABLC has been observed to be more nephrotoxic than L-AMP-B in patients at high risk for nephrotoxicity.

In adults with normal renal function prior to treatment; permanent functional impairment is uncommon even though permanent histological changes occur during short courses of C-AMB. Renal tubular acidosis and renal wasting of potassium and magnesium may also be seen several weeks after therapy. Supplemental potassium is required in one third of the patients on prolonged therapy.

Nephrotoxicity of Amphotericin B:

Impaired renal function occurs in 80% of cases. Recovery occurs once treatment is stopped. Hypokalemia occurs in 25% of cases.

Serum creatinine doubles by 57% during therapy.

Saline loading has decreased nephrotoxicity even in the absence of water or salt deprivation. Administration of one-liter normal saline on the day of C-AMB administration has been recommended for adults who are able to tolerate sodium load.

Immunosuppressants

Cyclosporine

It is an immunosuppressant used mainly for organ transplant. The dose of cyclosporine varies depending on the organ transplanted and other drugs used in the specific treatment protocol. Because of its nephrotoxicity, the initial dose should not be given before the transplant.

In renal transplant patients, therapeutic algorithms have been developed to delay cyclosporine introduction until a threshold renal function has been attained

Signs of rejection, renal or other toxicity and close monitoring of blood levels guide dosing.

Care has to be taken to differentiate renal toxicity and renal rejection. Ultrasound guided allograft biopsy helps to assess the basis for renal dysfunction.

Nephrotoxicity occurs in majority of patients and is the major reason for cessation or modification of therapy. Cyclosporine causes stimulation of transforming growth factor-β (TGF β) production. TGF β stimulates cells to increase biosynthesis of extracellular matrix component leading to interstitial fibrosis. Cyclosporine ADRs are more frequent on intravenous administration. Hence, it is discontinued as soon as the patient starts taking orally.

Anti-Viral Drugs

Cidofovir

It is the antiviral drug for treatment of human herpes, papilloma, pox and adenovirus infections. Nephrotoxicity is its principal dose-limiting side effect. Concurrent administration of nephrotoxic drugs (AGs, amphotericin B, foscarnet) is contraindicated. At least seven days should elapse before initiation of cidofovir treatment.

Foscarnet

It is indicated for herpes and HIV infection. Its major dose related toxicity is nephrotoxicity. Rise in serum creatinine occurs in 50% of patients, which is usually reversible after cessation of therapy. The risk factors include high doses, rapid infusion, dehydration, prior renal insufficiency and concurrent nephrotoxic drugs. Saline infusion reduces the risk of toxicity.

Adefovir

It is an antiviral drug used in the treatment of hepatitis B. Dose related nephrotoxicity and tubular dysfunction is observed which gets reversed months after discontinuation of therapy.

Glycopeptide Antibiotics

All glycopeptide antibiotics are nephrotoxic drugs.

Vancomycin

It gets excreted by glomerular filtration to an extent of 90%. It accumulates in renal impairment and dose should be reduced.

Dalbavancin

33% to 50% of it gets excreted unchanged by renal excretion. Hence, dose adjustment is required in renal disease.

Telavancin

As it is eliminated primarily by renal excretion, dose adjustment is required in renal disease. Telavancin is more nephrotoxic than Vancomycin.

Contrast media

It is administered intra-arterial or intravenously to provide radiographic delineation of the vascular system in organs like the heart and the brain. These agents appear to cause renal injury by direct toxicity to the renal tubular epithelial cells and reduced renal medullary blood flow (by constriction of the vasa recta). The nephrotoxicity of contrast media is dose dependent. High-risk patients include patients with preexisting reduction in medullary blood flow due to renal insufficiency, intravascular volume depletion, heart failure, diabetes and concurrent diuretic or non-steroidal anti-inflammatory drug (NSAIDs) use.

Tetracyclines

Tetracyclines and Glycylcyclines

The catabolic effect of tetracyclines aggravates azotemia in patients with renal disease. Minocycline, doxycycline and tigecycline produce less toxic renal effects than oxytetracycline and tetracycline.

Fanconi syndrome: Outdated tetracyclines can cause toxic effects on proximal renal tubules. The metabolites of tetracyclines are mainly responsible for this syndrome.

Biguanides

Phenformin and buformin, were withdrawn from use as they caused lactic acidosis. Metformin was the only biguanide in use as an oral hypoglycemic drug. There were no reports of lactic acidosis associated with metformin in conditions of poor tissue perfusion like sepsis, myocardial infarction or congestive heart failure.

Recent analysis has raised doubts about association of metformin with lactic acidosis as causal. Renal failure is a common comorbidity in patients with lactic acidosis associated with metformin use and plasma

metformin levels are inversely related to glomerular filtration rate (GFR) due to reduced clearance from the circulation. Levels rise above the usual therapeutic range when creatinine clearance drops below 40 ml/minute. Current guidelines suggest, metformin dose to be reduced when GFR falls below 45 ml/minute and to discontinue metformin if GFR falls below 30 ml/minute. It is important to assess renal functions before starting metformin and to monitor functions annually. Cationic drugs that are eliminated by renal tubular secretion can compete with metformin for common tubular transport system. Dose adjustment is necessary in patients on cationic drugs like cimetidine, furosemide, nifedipine or non-steroidal anti-inflammatory drugs (NSAIDs). All NSAIDs have been associated with renal and reno-vascular adverse events as they act by inhibiting prostaglandin synthesis. The NSAIDs have little effect on renal function in healthy human subjects. In clinical conditions (dehydration, congestive heart failure, hepatic cirrhosis, hypovolemia, chronic kidney disease and other states of activation of sympathetic or renin-angiotensin system) in which renal blood flow depends on the vasodilator prostaglandin (PGI), NSAIDs can predictably cause acute renal failure. NSAIDs impair prostaglandin (PG) induced inhibition of chloride reabsorption and actions of ADH leading to retention of salt and water. Inhibition of COX II derived PGs that regulate renal medullary blood flow lead to hypertension, congestive heart failure and a high risk of cardiovascular thrombotic events.

Analgesic Nephropathy

It consists of renal papillary necrosis and chronic interstitial nephritis. Inhibition of renal prostaglandin synthesis possibly is responsible for the slowly progressive end-stage renal failure. Risk factors include prolonged and massive overuse of analgesics and frequent urinary tract infections. Complete recovery occurs if recognized early and NSAIDs discontinued.

Angiotensin Converting Enzyme Inhibitors (ACEI)

Inhibition of ACE can induce acute renal insufficiency in bilateral renal artery stenosis, unilateral stenosis of a single remaining kidney, heart failure, volume depletion owing to diarrhea or diuretics. ACEI should be administered with caution in patients with intravascular volume depletion. These patients have reduced renal perfusion at baseline leading to a compensatory increase in renin and angiotensin II. This increase in angiotensin II is one of the physiological mechanisms by which glomerular filtration rate is maintained in them. Administration of ACEIs to these patients disrupts this auto regulatory mechanism leading to renal failure. ACEIs are a common cause of acute renal failure in patients with bilateral renal artery stenosis. In such patients GFR depends on angiotensin II mediated efferent arteriolar vasoconstriction. Acute renal failure occurs on starting these drugs but is reversible if the drug is stopped promptly. Hyperkalemia can also be severe because of reduced aldosterone secretion.

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