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PHARMACOTHERAPY OF COMORBID CONDITIONS IN PATIENTS ON HEMODIALYSIS.

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ABSTRACT

Chronic kidney disease (CKD) is one of the major causes of morbidity and mortality among noncommunicable diseases in India. Majority of the patient chronic kidney disease (CKD) also suffers from 2 to 4 comorbid conditions, hypertension, diabetes mellitus and coronary artery disease tops the list of these comorbid conditions and need an average of 6-8 medications that predispose these patients to medication related problem in the form of both therapeutic failure and drug toxicity mostly because of the ignorance of the prescribing physician about the pharmacokinetic and pharmacodynamic changes that occurs in the various stages of chronic kidney disease that needs drug dose and frequency adjustment especially in the patients of end stage renal disease, the general guidelines provided by different agencies for dose adjustment cannot be applied for all the patients because the pharmacokinetic and pharmacodynamic changes in all the patients are not same it depends on a large number of factors like age, sex, duration and severity of CKD and frequency and dose of hemodialysis received by these patients and also the fluid accumulation in between the subsequent hemodialysis etc. So individual dose adjustment depending on pharmacokinetic and pharmacodynamic changes in a patient will improve the quality and productivity of these patient.

KEY WORDS: CKD, Pharmacotherapy, hemodialysis.

INTRODUCTION

Non-communicable disease has become one of the leading cause of death in India, according to a nationwide survey (conducted in five states Assam, Bihar, Maharashtra, Rajasthan and

Tamil Nadu) by Indian council of medical research in the year-2003, non-communicable disease were responsible for 42% of all the deaths out of which genitourinary diseases were alone responsible for 3.8% of all the causes of death among noncommunicable diseases. The prevalence of genitourinary disease and deaths related to these diseases were maximum in the age group of 45 – 59years which is the main productive year of life especially in peoples living in rural areas and urban slums where if the earning member gets affected by these diseases it destroys the whole family as the majority of nephrology related services are available in private sector hospital that are out of reach from these population.

The major cause of death in urinary system disease is inadequate therapy in the patient of who develops renal failure.

The renal failure is broadly divided into acute renal failure (ARF) which is defined as the abrupt deterioration in renal function that results in inability of the kidney to regulate water and solute balance, acute renal failure is mainly caused by a decreased blood flow to the kidney due to severe infection, nephrotoxic drugs or stone in urinary tract, in majority of cases if ARF is discovered early enough, it can be reversed and the kidney can recover. The other form of renal failure is chronic renal failure (CRF) where kidney functions decreases slowly over time finally leading to end-stage renal disease when the patient needs renal replacement therapy in the form of dialysis or renal transplantation.

Chronic Kidney disease (CKD)

Chronic kidney disease is defined as the presence of kidney damage or decreased level of kidney function for a period of three months. CKD is a major public health problem and in the recent years the increasing number of diabetic patient especially in poor population in India is the biggest threat of increasing the number of patient who develops ESRD because of low health awareness of the poor population and unavailability of proper health care services to these population leading to improper control of diabetes mellitus causing rapid development of diabetic nephropathy and early development of end-stage renal disease requiring renal replacement therapy.

Chronic renal failure is a devastating medical, social and economic problem for patients and their families. There is no data on the true incidence and prevalence of chronic renal failure in the developing countries. Delayed diagnosis and failure of institution of measures to progression of renal failure results in a predominantly young ESRD population.

Stages of chronic kidney disease and their management

Usually kidney disease starts slowly and silently and progress over a number of years to a stage when the function of kidney is reduced to less than 15% of normal and the patient has to put on renal replacement therapy.

Depending on the severity of kidney damage and the level of decrease in the kidney function CKD is graded into five stages:

Stage-I CKD

there is evidence of kidney damage in the form of proteinuria, hematuria, genetic trait pointing to kidney disease (polycystic kidney disease) or an evidence of structural abnormality (renal dysgenesis, reflux nephropathy) but the glomerular filtration rate (GFR) is either normal or even increased ($\geq$ 90ml/min/1.73m^2) in this stage.

Stage-II CKD

there is evidence of kidney damage with mild decrease in GFR (60 – 89 ml/min/1.73m^2).

Management of stage I & II CKD

No specific treatment is needed but both in stage I & II especially with proteinuria the risk of cardiovascular morbidity and mortality is much higher and the patient must be encouraged some lifestyle modifications like quitting smoking, regular exercise anti-hyperlipidemic drugs if needed and strict control of blood pressure (130-139/90 mmHg but if proteinuria is present 120-129/80mmHg) is required.

The patients of stage I & II needs close monitoring to confirm that things are stable, a rise of creatinine by > 20% or a decrease in GFR of 5ml/min over 12 months needs further investigation.

Stage-III CKD and its management

there is moderate decrease in GFR (30 – 59ml/min/1.73m^2).

Management of stage III CKD

if creatinine and GFR is stable the management is based on identifying individual at risk of progression of renal disease.

Urine testing (for hematuria and proteinuria) and **imaging** (for exclusion of obstruction).

Estimation of creatinine and potassium

should be done every six monthly and if stable may be every 12 monthly a loss of GFR of more than 5ml/min over one year indicates deteriorating disease.

Hemoglobin estimation

as GFR falls there is a progressive fall of hemoglobin but renal anemia rarely becomes significant before stage IV CKD.

Management of cardiovascular risk factors

maintain a blood pressure of < 130/80 mm Hg especially if the patient is having proteinuria.

Medication review

regular review of nephrotoxic drugs that need dose adjustment with reduction in GFR.

Stage-IV CKD and its management

there is severe decrease in GFR (15 – 29 ml /min/1.73m^2).

Due to severe decline of renal function these patients may suffer from a series of symptoms and complications, they are at higher risk for developing uremia, anemia, bone diseases and cardiovascular complications.

Management of Stage-IV CKD

the basic aim of management of this stage is to prevent complications and protect kidney function and overall health of the patient to put off dialysis or transplant for as long as possible.

Regular monitoring of creatinine, potassium, calcium, phosphate and hemoglobin should be done.

Diet plan

patients of stage-IV CKD needs proper diet plan (diet low in protein, limiting phosphorus to keep the parathyroid hormone level normal will prevent bone disease also restriction of potassium consumption is helpful for these patients.

Stage-V CKD (end stage renal disease or kidney failure)

the GFR is decreased to less than 15 ml/min/1.73m^2.

Management of Stage-V CKD

the national kidney foundation guidelines recommended starting dialysis when kidney function drops to 15% or less. By doing everything possible to help prolong kidney function and overall health, the goal is to put off dialysis or renal transplant for as long as possible.

Renal replacement therapy

is the life supporting or life extending treatment of the patients of chronic renal failure.

Modalities of renal replacement therapy

the modalities of renal replacement therapy available for the treatment of ESRD includes renal transplantation, hemodialysis and peritoneal dialysis and hemofiltration.

Hemodialysis Dialysis

is the most commonly used modality of renal replacement therapy, it is the process of replacing non-endocrine function of the kidney in the patients of chronic renal failure.

At the best, hemodialysis provides removal of waste, removal of large quantity of accumulated fluid to avoid volume overload and to prevent congestive heart failure and pulmonary edema, correction of serum solutes (Na, K, Cl, HCO3, Ca, Mg, Phosphate, Urea, Creatinine and Uric acid etc.) and acid base balance without compensating for the endocrine (decreased erythropoietin and 1, 25-dihydroxyvitamin D3 production) and metabolic activities of the kidney.

The ultimate goal of hemodialysis is to improve health-related quality of life and to decrease morbidity and mortality.

The decision of putting a patient of end stage renal disease on hemodialysis is decided by the patient's condition (clinical features of uremia) biochemical abnormalities and resources for the treatment. Usually the presence uremic symptoms, hyperkalemia and metabolic acidosis that do not respond to conservative measures is the main indication of dialysis.

Pharmacotherapy in patients on hemodialysis

Patients of end-stage renal disease are on an average have 5 to 6 chronic medical conditions that require 8 -12 medications, the commonly reported co-morbid conditions are diabetes, hypertension, anemia, coronary artery disease and infectious diseases and most commonly

prescribed drugs are anti-hypertensive, anti-diabetics, antimicrobials, erythropoietin, iron preparations, calcium and phosphate analogues and vitamins.

Therefore keeping in view of the increasing frequency of patients having chronic renal failure with multiple disorders that need hemodialysis along with many other medications it is very difficult to avoid medication related problems in these patients unless proper pharmacodynamic and pharmacokinetic changes that occurs in these patient both in inter-dialysis period and intra-dialysis period are properly considered and an immediate feedback is provided to the prescribers for drug dosage adjustment where necessary.

Basically medication related problem in patients undergoing hemodialysis are:

(a) Accumulation of drug and its metabolites in the body

most of the drugs undergo hepatic biotransformation to more polar but less pharmacologically active compounds that require intact renal function for elimination, kidney apart from acting as an organ of elimination of drugs and its metabolites is also responsible for metabolism of some drugs, in the patients of hemodialysis these drugs and its toxic metabolites may accumulate in the body especially during inter-dialysis period that may cause toxicity. Some of the drugs (e.g. aminoglycoside antibiotics, H2-receptor antagonist, ACE inhibitor, digoxin and Lithium) are primarily eliminated unchanged through kidney that requires proper dose adjustment to avoid toxicity.

Metabolism of drug is also unpredictable in patients undergoing hemodialysis, metabolism of a drug by hydrolysis and reduction is slowed that again can lead to accumulation of drug in the body.

Drug dose adjustment in patients of hemodialysis

dose adjustment in dialysis patient is especially critical because parent compounds or active metabolites can accumulate and cause additional morbidity in these patient. Dose of a drug in renal failure patient can be adjusted by estimating renal function may by combined evaluation of serum creatinine value and patient characteristics. The individual elimination capacity of a drug in the individual patient may be calculated and dosage accordingly adjusted.

Loading dose

if given for drugs having long plasma half-life are not needed but if given for large volume of distribution should be used as such in these patients.

Maintenance dose

the plasma half –life of drugs that are mainly excreted unchanged through kidney is increased due to decreased elimination of drug, maintenance dose of these drugs should be reduced either by increasing the dosing interval (more useful for a drug with a wide therapeutic range and longer half-life) or by decreasing each single dose.

Clearance of a drug by dialysis

there are a long list of drugs that are removed from the body along with the waste products and fluid during the process of dialysis and if proper dose adjustment is not done there may be therapeutic failure.

Factors determining clearance of drugs by dialysis

can be grouped into drug factor and dialysis factors.

Drug factors determining drug clearance during hemodialysis

Molecular weight of the drug

the major processes by which drugs are cleared during hemodialysis is by diffusion (removal of drug by movement down its concentration gradient) the diffusion is greater with lower molecular weight (MW <1000Da) drugs, and most of the drug have molecular weight of less than 1000 Da, thus dialysis May cause more clearance of these drugs and if proper dose adjustment is not done this may lead to therapeutic failure, on the other hand drugs having large MW takes longer to equilibrate from intracellular to extracellular compartment in the body that may result in post dialysis rebound.

This problem can be minimized by using a large ultrafiltration that decreases the concentration gradient between blood and dialysate decreasing the diffusion of small molecular weight drugs.

Protein binding of a drug

high protein binding of drug decreases its clearance during dialysis but loss of protein during dialysis also increases the loss of protein bound drug, apart from loss of protein bound drug during dialysis, protein loss during dialysis causes decrease in plasma protein level that may increased amount of free drug in the plasma.

Volume of distribution of a drug

Most of the drugs with small volume of distribution (< 1 lit/kg) remains in the plasma so greater amount of drug is removed during dialysis but the drugs with large volume of distribution (> 2lit/kg) have lower concentration in the plasma and less amount is removed during dialysis but there is a larger tendency for rebound once hemodialysis stops. In short drugs with low MW, low volume of distribution and water soluble are most likely to be removed by hemodialysis and will require extra dosing.

The volume of distribution of water soluble drugs varies greatly during the inter dialysis period due to accumulation of large amount of fluid in the patient especially of developing country like India where because of economic reason most of the patient undergoes dialysis only twice or even once a week causing accumulation of large amount of fluid in inter-dialysis period making the proper monitoring of drug therapy very difficult.

Dialysis factors affecting the drug loss

the dialysis factors that affects the removal of drug during dialysis are the surface (pore size) of the dialyzer, dialysis membrane composition, dialysis flow rates and blood flow rates.

Measure of filtration of drug during hemodialysis (Sieving coefficient)

it is the ratio of drug concentration in the ultrafiltrate to the pre-filter plasma water concentration (drug in the arterial line). If the sieving coefficient is close to one the drug has relatively free passage across the filter.

Some of the important drugs having sieving coefficient of around one are amikacin, ampicillin, ceftazidim, digoxin. Gentamycin, metronidazole, procainamide, and vancomycin, all these drug needs dose adjustment in patient undergoing dialysis.

Some of the commonly used drug that do not need dose adjustment are amlodipine, felodipin, nimodipin, diltiazem, furosemide, ibuprofen, insulin, losartan, irbesartan, INH, rifampin, ketoconazole, labetalol, lidocaine, timolol, norfloxacin, pantoprazole, phenytoin, prednisone, iron dextran, iron sucrose, propranolol, quinine, ranitidine etc.

CONCLUSION

The quality of life of the patient undergoing hemodialysis is poor especially in developing countries like India and one of the reason for that is inadequate drug therapy for the comorbid condition due to lack of qualified nephrologist and clinical pharmacologist.

Every patient undergoing hemodialysis has unique pharmacokinetic and pharmacodynamic characteristic and the general guidelines provided by various national and international kidney foundations cannot be applied in all the patient equally. To improve the quality of life and productivity drug therapy for every patient undergoing hemodialysis should be considered separately based on the co-morbid conditions and frequency and adequacy of hemodialysis.

hemodialysis has unique pharmacodynamic and pharmacokinetic changes that need individualization of therapy that will improve the quality of life and productivity of these patients.

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