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A Review on Medications Taken During Haemodialysis

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ABSTRACT

Chronic Kidney Disease (CKD) has become a major cause of global morbidity and mortality even in developing countries. Worldwide, End-Stage Renal Disease (ESRD) has become a public health concern increasing the number of patients maintained on haemodialysis before renal transplantation. The presence of reduced kidney function in patients with ESRD alters drug disposition. This alteration necessitates appropriate individualization of drug therapy to avoid unnecessary drug accumulation and adverse drug effects. This article aims to review commonly prescribed medications in patients undergoing haemodialysis.

INTRODUCTION:

Chronic Kidney Disease (CKD) is a widely prevalent serious condition associated with premature mortality, decreased quality of life, and increased healthcare expenditures. (1) The irreversible advanced CKD leads to End-Stage Renal Disease (ESRD) where there is permanent loss of kidney function causing extreme mortality rates among this population. (2) In India, the rising incidence of CKD is likely to pose a major problem for both healthcare and the economy in future years. Indeed, it has been recently estimated that the age-based incidence rate of ESRD in India to be 229 per million population. (3) In CKD, there is an accumulation of toxins and excess water due to compromised renal function. Dialysis is considered the preferred treatment for the removal of waste and extra water from the blood. (4)Although kidney transplantation is the best choice of treatment for renal failure, resource constraints and shortage of kidney donations remain an issue. (5)

Dialysis is the transfer of uremic solutes from blood to an extracorporeal fluid (dialysate) by diffusion across a semi-permeable membrane. This may be done by pumping blood through a dialyzer containing a membrane and dialysate (haemodialysis), or by instilling dialysate into the peritoneal cavity and using the peritoneum itself as a membrane (peritoneal dialysis). Solute removal via haemodialysis is relatively efficient and so can be done intermittently – typically three times per week – whereas peritoneal dialysis is less efficient and so is usually required for 12–24 hours every day. (6)

Haemodialysis

Haemodialysis is a medical procedure to remove fluid and waste products from the blood and to correct electrolyte imbalances. This is accomplished using a machine and a dialyzer also referred to as an "artificial kidney. *Haemodialysis* is used to treat both acute (temporary) and chronic (permanent) kidney failure. The separation of wastes is done by creating a counter-current flow gradient, where blood flow is in one direction and the fluid of the dialyzer is in the opposite direction. (7)

Metabolic waste products, such as urea and creatinine, diffuse down the concentration gradient from the circulation into the dialysate sodium bicarbonate ($NaHCO_3$), sodium chloride (NaCl), acid concentrate, and deionized water. (8)

Peritoneal Dialysis

Peritoneal dialysis (PD) is a simple, "low-tech" form of renal replacement therapy. Peritoneal dialysis uses the peritoneum as a natural semipermeable membrane and removes waste and water into the dialysate (the material or fluid that passes through the membrane of the dialysis). (9)Compared with haemodialysis (HD), PD is more cost-effective, is less technically demanding, minimizes the exposure of patients to hospital-acquired infections, is more feasible in rural and remote settings. Despite the advantages associated with this modality, PD does have some limitations including catheter care, high frequency of dialysis in a day, bloating/pain, interference with sleep, etc. Therefore, haemodialysis is preferred over peritoneal dialysis in patients with ESRD. (10)

Principles of Prescribing

Prescribing to patients with ESRD is a complex process involving the determination of kidney function, consideration of changes in drug pharmacokinetics (PK) and pharmacodynamics (PD) as kidney function declines, and judicious use of therapies to manage uremic complications and other comorbid conditions. When prescribing for patients on dialysis, it is essential to refer a guideline to determine if the drug is subject to renal clearance and requires a dose adjustment. (10) The administration of multiple medications as well as poor compliance with drug regimens and drug interactions may contribute to drug-related problems. Appropriate drug selection for patients with ESRD is important to avoid unwanted drug effects and to ensure optimal patient outcomes. Inappropriate medication use can increase adverse drug effects as well as hospital stays, increased health care utilization, and costs. (11)

COMMONLY PRESCRIBED MEDICATIONS

1. RED BLOOD CELL STIMULATING AGENTS

Anaemia is common in patients with chronic kidney disease (CKD) and can have a significant impact on patient morbidity and mortality. The kidney is the organ primarily responsible for the regulation of erythropoiesis. Erythropoietin (EPO) is a hormone produced by the kidney that promotes the formation of red blood cells by the bone marrow. Renal failure is associated with a decreased erythropoietin output resulting in hypo proliferative anaemia. When a patient is on dialysis, it means that kidneys are not working well enough to make red blood cells. (11)

The medications that help to make red blood cells are:

- **Erythropoietin**

Replacement therapy with recombinant human erythropoietin (epoetin) has provided an effective treatment for patients with renal anaemia and has been shown to increase red blood cell (RBC) mass, reduce the need for RBC transfusions, and alleviate symptoms of anaemia in this population. Because epoetin has a relatively short circulating half-life, administration two to three times weekly is recommended. (12)

- **Darbepoetin**

Darbepoetin alfa is a new erythropoiesis-stimulating protein with a threefold longer terminal half-life than recombinant human erythropoietin (epoetin) in patients with chronic kidney disease (CKD). It is given once a week during hemodialysis. (12)(13)

2. IRON

Iron is an important mineral that the body uses for a variety of different functions, including making red blood cells that transport oxygen throughout the body. Iron deficiency anaemia is a common and clinically important concern in patients on chronic dialysis. (14) Patients with ESRD receiving treatment with erythropoiesis-stimulating agents (ESAs) are very prone to iron deficiency due to the increased demand for iron to support erythropoiesis. Chronic inflammation in these patients may lead to increased hepcidin production, in turn inhibiting both the uptake of dietary iron and the mobilization of stored iron from the reticuloendothelial system to circulating transferrin. Other causes of low iron include gastrointestinal bleeding, blood draws, surgery, dialysis treatment and not eating enough high iron foods because of poor appetite. As a result, iron supplementation is almost always necessary to maintain iron stores that are sufficient to enable optimal haematopoiesis with erythropoietin.(15)

Intravenous Iron sucrose

Oral iron therapy is not usually efficacious in haemodialysis patients. Therefore, parenteral iron replacement and maintenance are frequently advised. Intravenous iron sucrose can be given safely to dialysis patients as long as the therapy is performed according to international recommendations and guidelines. It replaces the iron in the body. Since an iron deficiency in ESRD patients develops primarily during the correction of renal anaemia by ESAs treatment,

approximately 150 mg of iron is necessary for an increase of 1 g/dl in haemoglobin level. It is given during each treatment through the dialysis machine for the first 4 weeks, then 1 or 2 times a month after that. (16)

Potential risk factors associated with intravenous iron therapy include acute allergic reactions such as rash, dyspnoea, wheezing, or even anaphylaxis, as well as long-term complications caused by the generation of powerful oxidant species, initiation and propagation of lipid peroxidation, endothelial dysfunction, propagation of vascular smooth muscle cell proliferation, and/or inhibition of cellular host defense. (17)

3. BLOOD PRESSURE MEDICATIONS

- **Management of patients with high blood pressure**

Fluids can build up between dialysis sessions causing high blood pressure. If blood pressure stays high for a long time, there is a higher chance of developing heart disease or having a heart attack or stroke. (18)

Different antihypertensive medications can help to control blood pressure in patients during dialysis.

While haemodialysis lowers blood pressure (BP) in most hypertensive end-stage renal disease (ESRD) patients, some patients exhibit a paradoxical increase in BP during haemodialysis. This increase in BP during haemodialysis, termed intradialytic hypertension, has been recognized for many decades. (19) Intradialytic hypertension is defined as an intradialytic increase in the systolic blood pressure by greater or equal than 10 mmHg or the mean arterial pressure by greater or equal than 15 mmHg.(20) Hypertension usually develops during the second or third hour of haemodialysis after significant ultrafiltration has taken place; the increase in the blood pressure is characterized as being resistant to ultrafiltration. (21) Aggravation of pre-existing hypertension or development of de novo hypertension might be related to the use of erythropoiesis-stimulating agents, which is managed by:

Acute management (22)

✓ If the patient has evidence of acute target organ damage, the blood pressure should be lowered by 30% or systolic blood pressure to less than 180/110 mmHg by using intravenous hydralazine or labetalol.

✓ If the patient is asymptomatic or has mild symptoms in the setting of a systolic blood pressure > 180/110 mmHg, a short-acting ACE inhibitor such as captopril is a reasonable initial approach. Other oral antihypertensive drugs that can be used include clonidine, a calcium channel blocker, or an adrenergic blocker (alpha- or beta-blockers).

✓ If pre-dialysis serum sodium level is < 140 mEq/L, dialysate sodium concentration may be decreased to minimize intradialytic sodium gain.

✓ If a patient develops edema, increase ultrafiltration rate to optimize fluid removal (optional).

- **Management of patients with low blood pressure**

Some patients may also have low blood pressure during dialysis. Consumption of sedatives just before the dialysis can dramatically lower BP during dialysis and should generally be avoided. (23) Many antihypertensive drugs that are removed by dialysis are often prescribed to be taken at night. It is necessary to check the patient's blood pressure during each dialysis session to make sure that blood pressure is under control. (24)

4. PHOSPHATE BINDERS

High levels of *phosphorus* in the *blood can* be dangerous for people with end-stage renal disease (ESRD). (25) It can be controlled by eating a low phosphate diet. Medications called phosphate binders are a commonly prescribed class of drug for patients on dialysis. They bind dietary phosphate in the gut and prevent it from being absorbed. (26)

There are four common types of phosphorus binders: calcium-based phosphorus binders; aluminum-free, calcium-free phosphorus binders; aluminum-based phosphorus binders; and magnesium-based phosphorus binders. (27) Among these, calcium-based phosphate binders (calcium carbonate) are the most common form of phosphate binder prescribed. It must be taken at the beginning of each meal. If calcium carbonate doesn't work well, doctors have also prescribed lanthanum carbonate or sevelamer. (28)

5. VITAMINS

Vitamins are playing a crucial role in multiple key metabolic pathways. Due to multiple factors, dialysis patients present very often hypo- or hypervitaminosis for a broad range of vitamins. Vitamin deficiencies in ESRD may originate from diet restriction, reduced

absorption by medications and co-morbidities, uremia-related alterations of metabolic pathways, and intradialytic losses. (29)

Vitamin B and C are lost during dialysis. There is a non-selective intradialytic loss of micro- and macronutrients, deranged intracellular kinetics, and gastrointestinal malabsorption due to uraemia. Frequent treatment with antibiotics due to infections associated with the acquired uremia-related immunosuppression may derange the vitamin-producing intestinal microflora. Certain agents prescribed in the context of renal failure or other conditions may reduce the absorption of vitamins from the gastrointestinal tract. These factors may deplete a dialysis patient from vitamins, especially the ones with antioxidant activity that may be associated with cardioprotective properties. In other cases, vitamins metabolized and excreted by the kidneys may be accumulated and exert toxic effects. The most common vitamin deficiencies observed in dialysis patients include those for vitamin C (ascorbate), folate, vitamin B_6 (pyridoxine), and 1,25-dihydroxycholecalciferol (calcitriol). (30)

- **Pyridoxine (B6)**

Pyridoxine (B_6) is a family of compounds that, unlike other water-soluble vitamins, can be stored in muscles. It is important for the metabolism of amino acids and fatty acids and influences cognitive development, immune function as well as steroid synthesis. The symptoms of B_6 deficiency include weakness, irritability, insomnia and in advanced stages, failure to grow, motor function impairment, convulsions, and immunosuppression. Vitamin B_6deficiency is prevalent within the dialysis population and is known to cause sideroblastic anaemia in experimental animals. (30) Toxic symptoms include neuromuscular disorders and nerve damage leading to numbness and muscle weakness. In dialysis patients, it has been shown that pyridoxine supplementation with 300 mg I.V. three times a week may significantly correct the high levels of total cholesterol, triglyceride, and LDL, and the low HDL. The RDA for vitamin B_6 is 1.3 mg/d for adult males and females through age 50. This daily dose of pyridoxine should be higher in haemodialysis patients as they present increased erythropoietin activity associated with the use of erythropoietin and there are some drugs and other substances that interfere with pyridoxine metabolism. (32) In a study on anaemic dialysis patients, the addition of pyridoxine in the conventional iron treatment has led to a more solid and sustainable correction of haemoglobin levels. Fifty milligrams of pyridoxine hydrochloride per three times a week post-dialysis seem to correct the serum levels of the B_6 metabolite glutamic oxaloacetic transaminase of the erythrocytes and a daily dose of

100 mg/d along with supraphysiologic doses of vitamin B_{12} and folic acid have led to the normalization of the serum homocysteine levels in haemodialysis as well as peritoneal dialysis patients. (33)

- **Vitamin C**

Vitamin C (Vit C) is the most abundant and effective water-soluble antioxidant in human plasma. Vitamin C deficiency is very common in dialysis patients mainly because of low dietary intake, losses during dialysis, and accelerated catabolism. Low levels of Vit C may have clinical consequences and associations with increased cardiovascular morbidity and mortality have been found. (34) It is an antioxidant that participates in the formation of collagen, serves as a matrix to form teeth and bone, is important in wound healing, and participates in the production of norepinephrine and thyroxin. It facilitates iron absorption and increases the resistance to infections. Its deficiency causes scurvy and toxicity symptoms to include nausea, vomiting, and diarrhoea. RDA for vitamin C is 90 mg/d for adult males and 75 mg/d for adult females. (35)

Ascorbic acid interacts with multiple pharmacological agents. It is found in fruits and vegetables, the foods that are usually restricted in dialysis patients in the context of a low potassium diet. The patients on haemodialysis and peritoneal dialysis usually present with low serum vitamin C levels. (36)

A dose of 500 mg per post-dialysis thrice-weekly has led to sustainably normal levels of vitamin C in haemodialysis patients. A daily dose of 250 mg can significantly protect the hemodialysis patients from muscle cramps and its combination with vitamin E has an additional effect on that matter. (37)

- **Vitamin D**

Vitamin D (calciferol) can be synthesized in the body when exposed to sunlight. It promotes cell differentiation and its chief role is the increase of calcium availability for bone mineralization and growth. Deficiencies may occur as a result of hepatic or renal failure and the symptoms are those of calcium deficiencies. For dialysis patients, it is necessary to measure serum 25-hydroxy-vitamin D3 regularly to substitute as needed. (38) Vitamin D deficiency (<20 ng/mL) and insufficiency (20–29 ng/mL) are common among patients with chronic kidney disease (CKD) or undergoing dialysis. Together with the progressive decline of serum calcitriol, vitamin D deficiency leads to secondary hyperparathyroidism (SHPT) and

its complications, tertiary hyperparathyroidism, and hypercalcemia, which require surgical parathyroidectomy or calcimimetics. (39) Treatment with vitamin D2 or D3 derivatives allows for the reduction of vitamin D deficiency, better control of mineral metabolism with less use of active vitamin D, attenuation of inflammation, reduced dosing of erythropoiesis-stimulating agents, and possibly improvement of cardiac function. (40) (41)

6. ANTIBIOTICS

Infection is second to cardiovascular disease as a cause of death in patients with end-stage renal disease (ESRD), and septicemia causes a majority of these infectious deaths. (42) Non-access-related infections among dialysis patients include infections of the upper and lower respiratory tract, gastrointestinal infections, including hepatitis and Clostridium difficile colitis, genitourinary tract infections, cellulitis and osteomyelitis, infections due to antibiotic-resistant organisms, and tuberculosis. Advancing age, diabetes mellitus, and uremia as a cause of acquired immune deficiency contribute to the high prevalence of infections in ESRD. Other factors that predispose these patients to infections include breaches in sterility during water treatment and distribution and dialysate delivery, dialyzer reuse, and failure to adequately follow maintenance recommendations. (43)

Antibiotics are medicines used to treat or prevent an infection. Most antibiotics are eliminated via either hepatic or renal mechanisms, and the clinician should use this knowledge to select an antibiotic with the proper spectrum for the patient. So the majority of the antibiotics require dose adjustment in patients receiving dialysis. Therapeutic Guidelines: Antibiotic provides a comprehensive and user-friendly. Drugs like quinolones, sulfamethoxazole with trimethoprim, glycopeptides, and aminoglycosides require significant dose reductions. Trimethoprim should be avoided in patients due to the risk of hyperkalemia and bone marrow suppression. (44) Nitrofurantoin is primarily renally excreted and relies on urinary concentration to achieve its effect. It is rarely associated with neurotoxicity and life-threatening pulmonary toxicity. Despite recent support for extending its use in chronic kidney disease, it should be avoided in patients on dialysis. Cephalosporins and penicillins have wider therapeutic indices and vary in the need for dose adjustment. (45)Once-daily doses should be prescribed after haemodialysis. Patients with CKD may have alterations in their protein binding, volumes of distribution, kidney clearance, and nonrenal clearance that necessitate antibiotic dose adjustments to prevent the development of toxicity. Knowledge of a drug's pharmacodynamics, defined as the relationship between drug exposure and

antibacterial efficacy, provides some guidance regarding the optimal way to make dose adjustments. (46) Different pharmacodynamics goals, such as maximizing the time that free (unbound) drug concentrations spend above the minimum inhibitory concentration (MIC) for time-dependent drugs (*e.g.*, *β*-lactams) or maximizing the free peak-to-MIC ratio for concentration-dependent antibiotics (*e.g.*, aminoglycosides), require different adjustment strategies; for instance, decreasing the dose while maintaining normal dosing frequency or giving normal (or even larger) doses less frequently, respectively. Patients receiving haemodialysis have other important prescribing considerations as well. The nephrologist or patient may prefer to receive antibiotics that can be administered intravenously toward the end of a dialysis session. (48)

CONCLUSION:

Prescribing for patients who are on haemodialysis can be challenging. Recognizing that patients on dialysis are more prone to drug toxicity is the first step in avoiding harm. It is very essential to refer a standard guideline to determine if the drug is subject to renal clearance and requires a dose adjustment. Strategies to improve prescribing of drugs such as the development of a simplified guide for dose adjustment of commonly prescribed drugs and pharmacist involvement in drug therapy monitoring should be considered.

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