World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

A REVIEW ON DIURETICS

***Prof. Sharma Shubham**

Assistant Professor, Department of Pharmacy, Shri G S Institute of Technology and Science, Indore (M.P.)

***Corresponding Author: Prof. Sharma Shubham**
Assistant Professor, Department of Pharmacy, Shri G S Institute of Technology and Science, Indore (M.P.)

Article Received on 12/01/2020 **Article Revised on 03/02/2020** **Article Accepted on 24/02/2020**

ABSTRACT
Diuretic drugs continue to attract the interest of renal physiologists not only for their intrinsic tubular effects but equally importantly for the insight that such studies provide into normal and abnormal mechanisms of renal function. Diuretics are the drugs which cause a net loss of sodium and water in urine. Diuretics are among the most widely prescribed drugs. Application of diuretics in the management of hypertension has outstripped their use in edema. Availability of diuretics has also had a major impact on the understanding of renal physiology.

INTRODUCTION

The use of diuretics for therapeutic purposes is not new. They were used for the treatment of dropsy as early as 16th century. Diuretic drugs increase urine output by the kidney by altering sodium handling. Diuretics increase urinary excretion of water and electrolytes and are used to relieve oedema associated with heart failure, nephrotic syndrome or hepatic cirrhosis. Some diuretics are used at lower doses to reduce raised blood pressure. Osmotic diuretics are mainly used to treat cerebral oedema, and also to lower raised intraocular pressure. Most diuretics increase urine volume by inhibiting the reabsorption of sodium and chloride ions in the renal tubule; they also modify renal handling of potassium, calcium, magnesium and urate. Osmotic diuretics act differently; they cause an increase in urine volume by an osmotic effect.

Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system. Diuretic use in clinical practice spans conditions like edema, hypertension, metabolic acidosis and hyperkalaemia. Patients with nephropathy or heart failure may have a 10 to 30% increase in extracellular and blood volume, even in the absence of overt edema.

Electrolyte imbalance: The adverse effects of diuretic therapy are mainly due to the fluid and electrolyte imbalance induced by the drugs. Hyponatraemia is an adverse effect of all diuretics. The risk of hypokalaemia, which may occur with both thiazide and loop diuretics, depends more on the duration of action than on potency and is thus greater with thiazides than with loop diuretics (when given in equipotent doses). Potassium sparing diuretics can cause hyperkalaemia. Other electrolyte disturbances include hypercalcaemia (thiazides), hypocalcaemia (loop diuretics) and hypomagnesaemia (thiazide and loop diuretics). Symptoms of fluid and electrolyte imbalance include dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, restlessness, seizures, confusion, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias.

Elderly: The elderly are more susceptible to electrolyte imbalance than younger patients. Treatment should begin with a lower initial dose of the diuretic (commonly about 50% of the adult dose) and then adjusted carefully according to renal function, plasma electrolytes and diuretic response.

Classification: Multiple classes of diuretics are available for use including loop diuretics, thiazides and potassium sparing diuretics. The level of GFR and need and urgency for reduction in ECF volume dictates the choice of diuretic agent.

Thiazide diuretics: Thiazide diuretics, such as hydrochlorothiazide, are moderately potent and act by inhibiting sodium and chloride reabsorption at the beginning of the distal convoluted tubule. They produce diuresis within 1–2 hours of oral administration and most have a duration of action of 12–24 hours. Thiazide diuretics are used in the management of oedema associated with mild to moderate congestive heart failure, renal dysfunction or hepatic disease; however, thiazides are not effective in patients with poor renal function (creatinine clearance of less than 30 ml per minute). In severe fluid retention a loop diuretic may be necessary. In hypertension, a thiazide diuretic is used at a low dose to lower blood pressure with very little

biochemical disturbance; the maximum therapeutic effect may not be seen for several weeks.

Higher doses should not be used because they do not necessarily increase the hypotensive response but may cause marked changes in plasma potassium, magnesium, uric acid, glucose and lipids. If a thiazide alone does not lower blood pressure adequately, it may be used in combination with another antihypertensive such as a beta-adrenoceptor antagonist. Urinary excretion of calcium is reduced by thiazide diuretics and this property is occasionally utilized in the treatment of idiopathic hypercalciuria in patients with calcium-containing calculi.

Paradoxically, thiazide diuretics are used in the treatment of diabetes insipidus, since in this disease they reduce urine volume. Thiazide diuretics, especially in high doses, produce a marked increase in potassium excretion which may cause hypokalaemia; this is dangerous in patients with severe coronary artery disease and those being treated with cardiac glycosides. In hepatic failure hypokalaemia can precipitate encephalopathy, particularly in alcoholic cirrhosis.

Potassium-sparing diuretics are used as a more effective alternative to potassium supplements for prevention of hypokalaemia induced by thiazide diuretics; however supplementation with potassium in any form is seldom necessary with the smaller doses of diuretics used to treat hypertension.

Hydrochlorothiazide: Hydrochlorothiazide is a representative thiazide diuretic. Various drugs can serve as alternatives.

***Tablets*:** Hydrochlorothiazide, 25 mg, 50 mg.

Uses: Oedema; diabetes insipidus; hypertension, heart failure.

Contraindications: Severe renal or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia, Addison disease.

Precautions: Renal, hepatic impairment, pregnancy, breastfeeding, elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria; interactions.

Dosage: Orally ADULT 12.5–25 mg daily; ELDERLY initially 12.5 mg daily Oedema, by mouth, ADULT initially 25 mg daily on rising, increasing to 50 mg daily if necessary; ELDERLY initially 12.5 mg daily Severe oedema in patients unable to tolerate loop diuretics, by mouth, ADULT up to 100 mg either daily or on alternate days (maximum 100 mg daily) Nephrogenic diabetes insipidus, by mouth, ADULT initially up to 100 mg daily.

Adverse effects: Hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis (for symptoms of fluid and electrolyte imbalance see introductory notes); hypercalcaemia; hyperglycaemia; hyperuricaemia, gout; rash, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible), blood disorders (including neutropenia, thrombocytopenia); pancreatitis, intrahepatic cholestasis and hypersensitivity reactions (including pneumonitis, pulmonary oedema, severe skin reactions) also reported; acute renal failure.

Loop diuretics: Loop diuretics, or high-ceiling diuretics, such as furosemide, are the most potent and rapidly produce an intense dose-dependent diuresis of relatively short duration. Oral furosemide produces diuresis within 30–60 minutes of administration, with the maximum diuretic effect in 1–2 hours. The diuretic action lasts for 4–6 hours. Intravenous furosemide produces diuresis within 5 minutes, with the maximum diuretic effect in 20–60 minutes and diuresis complete within 2 hours.

Loop diuretics inhibit reabsorption from the ascending loop of Henle in the renal tubule and are useful, particularly in situations where rapid and effective diuresis is needed such as reduction of acute pulmonary oedema due to left ventricular failure. They are also used to treat oedema associated with renal and hepatic disorders and are used in high doses in the management of oliguria due to chronic renal insufficiency. Loop diuretics may be effective in patients unresponsive to thiazide diuretics.

Because of their shorter duration of action, the risk of hypokalaemia may be less with loop diuretics than with thiazide diuretics; if required, potassium-sparing diuretics may be used for prevention of hypokalaemia. Loop diuretics may cause hypovolaemia and excessive use can produce severe dehydration with the possibility of circulatory collapse. Furosemide may cause hyperuricaemia and precipitate attacks of gout. Rapid high-dose injection or infusion of furosemide may cause tinnitus and even permanent deafness.

Furosemide: Furosemide is a representative loop diuretic. Various drugs can serve as alternatives.

Tablets: furosemide 40 mg/ Injection (Solution for injection), furosemide 10 mg/ml, 2-ml ampoule.

Uses: Oedema; oliguria due to renal failure.

Contraindications: Renal failure with anuria; precomatose states associated with liver cirrhosis.

Precautions: Monitor electrolytes particularly potassium and sodium; hypotension; elderly (reduce dose);

pregnancy, breastfeeding, correct hypovolaemia before using in oliguria; renal impairment, hepatic impairment; prostatic enlargement; porphyria.

***Dosage*:** Oedema, by mouth, ADULT initially 40 mg daily on rising; maintenance, 20–40 mg daily; may be increased to 80 mg daily or more in resistant oedema; CHILD 1–3 mg/kg daily (maximum 40 mg daily).

Adverse effects: Hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis (for symptoms of fluid and electrolyte imbalance, see introductory notes), increased calcium excretion, hypovolaemia, hyperglycaemia (but less often than with thiazide diuretics); temporary increase in plasma cholesterol and triglyceride concentration; less commonly hyperuricaemia and gout; rarely rash, photosensitivity, bone marrow depression (withdraw treatment), pancreatitis (with large parenteral doses), tinnitus and deafness.

Potassium-sparing diuretics: Potassium-sparing diuretics include amiloride and spironolactone; they are weak diuretics and reduce potassium excretion and increase sodium excretion in the distal tubule. Amiloride acts about 2 hours after oral administration, reaching a peak in 6–10 hours and persisting for about 24 hours. Spironolactone, which acts by antagonising aldosterone, has a relatively slow onset of action requiring 2–3 days to achieve maximum diuretic effect, and a similar period of 2–3 days for diuresis to cease after discontinuation of treatment.

Amiloride may be used alone, but its principal use is in combination with a thiazide or a loop diuretic to conserve potassium during treatment of congestive heart failure or hepatic cirrhosis with ascites.

Spironolactone is used in the treatment of refractory oedema due to heart failure, hepatic cirrhosis (with or without ascites), nephrotic syndrome and ascites associated with malignancy. It is frequently given with a thiazide or a loop diuretic, helping to conserve potassium in those at risk from hypokalaemia. A low dose of spironolactone is beneficial in severe heart failure in patients who are already taking an ACE inhibitor and a diuretic. Spironolactone is used in the diagnosis and treatment of primary hyperaldosteronism; presumptive evidence for diagnosis is provided by correction of hypokalaemia and of hypertension.

The most dangerous adverse effect of potassium-sparing diuretics, such as amiloride or spironolactone, is hyperkalaemia, which can be life-threatening. These diuretics are thus best avoided or used very carefully in patients who have or may develop hyperkalaemia, such as those with renal failure, patients receiving other potassium sparing diuretics and patients taking ACE inhibitors or potassium supplements.

Amiloride hydrochloride (Tablets): Amiloride hydrochloride 5 mg.

***Uses*:** Oedema associated with heart failure or hepatic cirrhosis (with ascites), usually with thiazide or loop diuretic.

Contraindications: Hyperkalaemia; renal failure.

Precautions: Monitor electrolytes, particularly potassium; renal impairment, diabetes mellitus; elderly (reduce dose); pregnancy and breastfeeding.

Dosage: Oedema, used alone, by mouth, initially 10 mg daily in 1 or 2 divided doses, adjusted according to response (maximum 20 mg daily).

Combined with a thiazide or a loop diuretic, by mouth, initially 5 mg daily, increasing to 10 mg if necessary (maximum 20 mg daily).

Adverse effects: Hyperkalaemia, hyponatreamia (for symptoms of fluid and electrolyte imbalance see introductory notes), diarrhoea, constipation, anorexia; paraesthesia, dizziness, minor psychiatric or visual disturbances; rash, pruritus; rise in blood urea nitrogen.

Osmotic diuretics Osmotic diuretics, such as mannitol, are administered in sufficiently large doses to raise the osmolarity of plasma and renal tubular fluid. Osmotic diuretics are used to reduce or prevent cerebral oedema, to reduce raised intraocular pressure or to treat disequilibrium syndrome. Mannitol is also used to control intraocular pressure during acute attacks of glaucoma. Reduction of cerebrospinal and intraocular fluid pressure occurs within 15 minutes of the start of infusion and lasts for 3–8 hours after the infusion has been discontinued; diuresis occurs after 1–3 hours.

Circulatory overload due to expansion of extracellular fluid is a serious adverse effect of mannitol; as a consequence, pulmonary oedema can be precipitated in patients with diminished cardiac reserve, and acute water intoxication may occur in patients with inadequate urine flow.

Mannitol Infusion (Solution for infusion): Mannitol 10%, 20%.

Uses: Cerebral oedema; raised intraocular pressure (emergency treatment or before surgery)

Contraindications: Pulmonary oedema; intracranial bleeding (except during craniotomy); severe congestive heart failure; metabolic oedema with abnormal capillary fragility; severe dehydration; renal failure (unless test dose produces diuresis).

Precautions: Monitor fluid and electrolyte balance; monitor renal function.

Dosage: Test dose if patient oliguric or renal function is inadequate, by intravenous infusion, as a 20% solution, 200 mg/kg body weight infused over 3–5 minutes; repeat test dose if urine output less than 30–50 ml/hour; if response inadequate after second test dose, re-evaluate patient.

Raised intracranial or intraocular pressure, by intravenous infusion, as a 20% solution infused over 30–60 minutes, 0.25–2 g/kg body weight.

Cerebral oedema, by intravenous infusion, as a 20% solution infused rapidly, 1 g/kg body weight.

Adverse effects: Fluid and electrolyte imbalance (for symptoms see introductory notes); circulatory overload, acidosis; pulmonary oedema particularly in diminished cardiac reserve; chills, fever, chest pain, dizziness, visual disturbances; hypertension; urticaria, hypersensitivity reactions; extravasation may cause oedema, skin necrosis, thrombophlebitis; rarely, acute renal failure (large doses).

CONCLUSION

The availability of many different diuretic drugs that can selectively inhibit one or more of a variety of transport processes within the nephron provides a wide range of options that can be rationally used in the treatment of edema states and nonedematous disorders. Caution must be exercised before the results at a segmental level of the nephron can be extrapolated to whole kidney in vivo performance. For instance, hemodynamic effects, changes in ECF volume, intratubular pressure, tubular fluid flow rate, or electrolyte composition, etc., may all exert effects on solute transport independently of any direct effect of the drug in a particular nephron segment. Many questions remain unanswered. The effects of certain diuretics upon proximal tubular transport are still unsettled and the results of in vivo experiments have not been reconciled with in vitro studies in the isolated perfused tubule. The mechanism whereby carbonic anhydrase inhibitors affect sodium and chloride transport is still unclear as is the extent to which such effects can account for the proximal action of thiazide diuretics. The answers to these and many other issues that have been raised by such studies require much further work and will undoubtedly contribute to a better understanding of the physiology of the kidney.

REFERENCE

1. Meng K, O'dea K: Peritubular and intraluminal concentrations of diuretics effecting isotonic fluid absorption in the kidney tubule, Pharmacology, 1973; 9: 193—200.
2. Grantham J: Sodium transport in isolated renal tubules in Modern Diuretic Therapy in the Treatment of Cardiovascular and Renal Diseases, edited by lamt af, Wilson GM, Amsterdam, Exerpta Medica, 1973: 220—226 .
3. Barratt U, Rector FC, Kokko JP, Seldin DW: Factors governing the transepithelial potential difference across the proximal tubule of the rat kidney. J C/in Invest, 1974; 53: 454—464.
4. Fromter E, Gessner K: Effect of inhibitors and diuretics on electrical potential differences in rat kidney proximal tubule, Pfluegers Arch, 1975; 357: 209—224.
5. K0kk0 JP, Burg MB, Orloff J: Characteristics of NaCI and water transport in the renal proximal tubule. J 'lin Invest, 1971; 50: 69—76.
6. Lutz MD, Cardinal J, Burg MB: Electrical resistance of renal proximal tubule perfused in vitro. Am J Physiol., 1973; 225: 729—734.
7. Seely IF, Variation in electrical resistance along length of rat proximal convoluted tubule. Am J Physiol., 1973; 225: 48—57?
8. Fromter e, Gessner K: Active transport potentials, membrane diffusion potentials and Streaming potentials across rat kidney proximal tubule. Pfluegers Arch., 1974; 35(1): 85—98.
9. Cardinal J, Lutz MD, Burg, Orloff j: Lack of relationship of potential difference to fluid absorption in the proximal renal tubule. Kidney In!, 1975; 7: 94—102.
10. Fromter E: Electrophysiology and isotonic fluid absorption of proximal tubules of mammalian kidney in Physiology, edited by THURAU K, Baltimore, University Park Press, 1974, series I, 6: 1—38.
11. Sciiafer, Patlak, Andreoli: A component of fluid absorption linked to passive ion flows in the superficial pars recta. J Gen Physiol., 1975; 66: 445—471.
12. Edwards BR, Baer, Sutton, Dirks: Micropuncture study of diuretic effects on sodium and calcium reabsorption in the dog nephron. J ('un Invest, 1973; 52: 2418—2427.
13. Knox FG, wright fs, Howard's ss, Berliner rw: Effect of furosemide on sodium reabsorption by proximal tubule of the dog. Am i Physiol., 1969; 217: 192—198.
14. Morgan t, Tadokoro m, martin d, Berliner rw: Effect of furosemide on Na and K transport studied by micro perfusion of the rat nephron. Am J Physiol., 1970; 218: 292—297.
15. Hoizgreve u: The pattern of inhibition of proximal tubular reabsorption by diuretics renal transport and diuretics in Renal Transport and Diuretics, edited by thurau k, jailsmarker U, New York, Springer Verlag, 1969: 229—234 .
16. Burg M, Stoner L C, Cardinal J, Green N: Furosemide effect on isolated perfused tubules. Am i Physiol., 1973; 225: 1 19—124.
17. Deetjen P: Micropuncture studies on site and mode of diuretic action of furosemide. Ann NY Acad Sci., 1966; 139: 408—415.
18. Evanson RL, Lockhart EA, disks JI-l: Effect of mercurial diuretics on tubular sodium and potassium

transport in the dog. Am J Physiol., 1972; 222: 282—289.
19. Clapp JR, Robinson RR: Distal site of action of diuretic drugs in the dog nephron. Am i Physiol., 1968; 215: 228—235.
20. Rocha AS, Kokko JP: Sodium chloride and water transport in the medullary thick ascending limb of Henle. I C/in Invest, 1973; 52: 612—623.
21. Burg M, Green N: Function of the thick ascending limb of Henle's loop. Am J Physiol., 1973; 224: 659—668.
22. Burg M, Green N: Effect of ethacrynic acid on the thick ascending limb of Henle's loop. Kidney mt, 1973; 4: 301—308.
23. Burg M, Green N: Effect of Mersalyl on the thick ascending limb of Henle's loop. Kidney mt., 1973; 4: 245—251.
24. Burg M: The mechanism of action of diuretics in renal tubules in Recent Advances in Renal Physiology and Pharmacology. Edited by wesson lg, fanelli gm jr, Baltimore Park Press, 1974: 99—109.
25. Goldberg m: The renal physiology of diuretics, chapter 28, in Handbook of Physiology, edited by orloff j, berliner rw, Washington, American Physiological Society, 1973: 1003—1031.
26. Duarte CG, Chomety F, Gifiiisuii G: Effect of amiloride, ouabain and furosemide on distal tubular function in the rat. Am i I'hysio/., 1971; 22(1): 632—639.
27. Wiederholt M, Sullivan WI, Giebisch G: Potassium and sodium transport across single distal tubules of amphiuma. I Gen Physiol., 1971; 57: 495—525.
28. Hieriiolzer K, Wiederholt M, Holzgreve H, Gifisisch G, Klose RM, Windhager: Micropuncture study of renal transtubular concentration gradients of sodium and potassium in adrenalectomized rats. Pfluegers Arch., 1965; 285: 193-210.
29. Herhoi, zer K: Intrarenal action of stcriod hormones on sodium transport in renal transport and diuretics, edited by thurau k, jahrmarker h, New York, Springer Verlag. 1969: 153—171.
30. Stoner IC, Burg MB, Orioff J: Ion transport in cortical collecting tubule, effect of amiloride. Am J Physiol., 1974; 227: 453—459.