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Pharmaceutical Sciences **Review Article……!!!**

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DIURETICS: A REVIEW

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ABSTRACT

Diuretics have been recommended as first-line treatment of hypertension and are also valuable in the management of hypervolemia and electrolyte disorders. This review summarizes the key features of the most commonly used diuretics. We then provide an update of clinical trials for diuretics during the past 5 years. Compared to other classes of medications, thiazide diuretics are at least as effective in reducing cardiovascular events (CVEs) in patients with hypertension and are more effective than β-blockers and angiotensin-converting enzyme inhibitors in reducing stroke. Observational cohort data and a network analysis have shown that CVEs are lowered by one-fifth from chlorthalidone when compared to the commonly used thiazide, hydrochlorothiazide. Relative to placebo, chlorthalidone increases life expectancy

INTRODUCTION

Diuretics play a significant role in pharmacology and treatment options in medicine. This paper aims to review and evaluate the clinical use of diuretics in conditions that lead to fluid overload in the body such as cardiac failure, cirrhosis and nephrotic syndrome. To know the principles of treatment it is essential to understand the underlying pathophysiological mechanisms that cause the need of diuretics in the human body. Various classes of diuretics exists, eachhaving a unique mode of action. A systemic approach for management is recommended based on the current guidelines, starting from thiazides and proceeding to loop diuretics. The first condition for discussion in the paper is cardiac failure. Treatment of ascites in liver cirrhosis with spironolactone as the primary agent is highlighted with further therapeutic options. Lastly, management choices for nephritic syndrome are discussed and recommended beginning from basic restriction to combined diuretic. (1)

Clinical pharmacology in diuretic use

Diuretics are among the most commonly prescribed drugs and although effective, they are often used to treat patients at substantial risk for complications making it especially important to understand and appreciate their pharmacokinetics and pharmacodynamics. Although thje available diuretic drugs posses distinctive pharmacokinetic and pharmacodynamic properties that affect both response and potential for adverse effects, many clinicians use them in a stereotyped manner , reducing effectiveness and potentially increasing side effects . diuretics have many uses but this review will focus on diuretics to treat extracellular fluid (ECF) volume expansion and edema the reader is referred elsewhere for discussion of diuretic treatment of hypertension , kidney stones, and other conditions. (2)

Overcoming diuretic resistance in edematous status

Fluid overload refractory to conventional treatment with LD can complicate acute or chronic heart failure management. Diuretic resistance in heart failure results from an interaction between the pathophysiology of sodium retention in heart failure and the renal response to diuretic therapy. (3) By eliciting significant counter regulatory responses during acute and chronic use, several effects such as the “breaking phenomenon”. Post diuretic effect , rebound sodium retention and renal adaptation lead to diuretic resistance. The breaking phenomenon describes an acute reduction in diuretic efficacy with repeated LD

dosing, while the post diuretic effect refers to increased sodium retention after the LD has worn off. Rebound sodium retention occurs when chronic LD use leads to increase distal nephron sodium reabsorption. Renal adaptation occurs with prolonged exposure to LD and is described as hypertrophy and hyper function of distal tubule cells causing increased sodium uptake and aldosterone secretion. Which markedly limits the response to LD. (4, 5). Distal tubule hypertrophy also appears to be an important contributor to rebound sodium retention and reduced response to chronic LD therapy over time (6). The activities of different diuretics should be considered to overcome the potential problems with diuretic resistance.

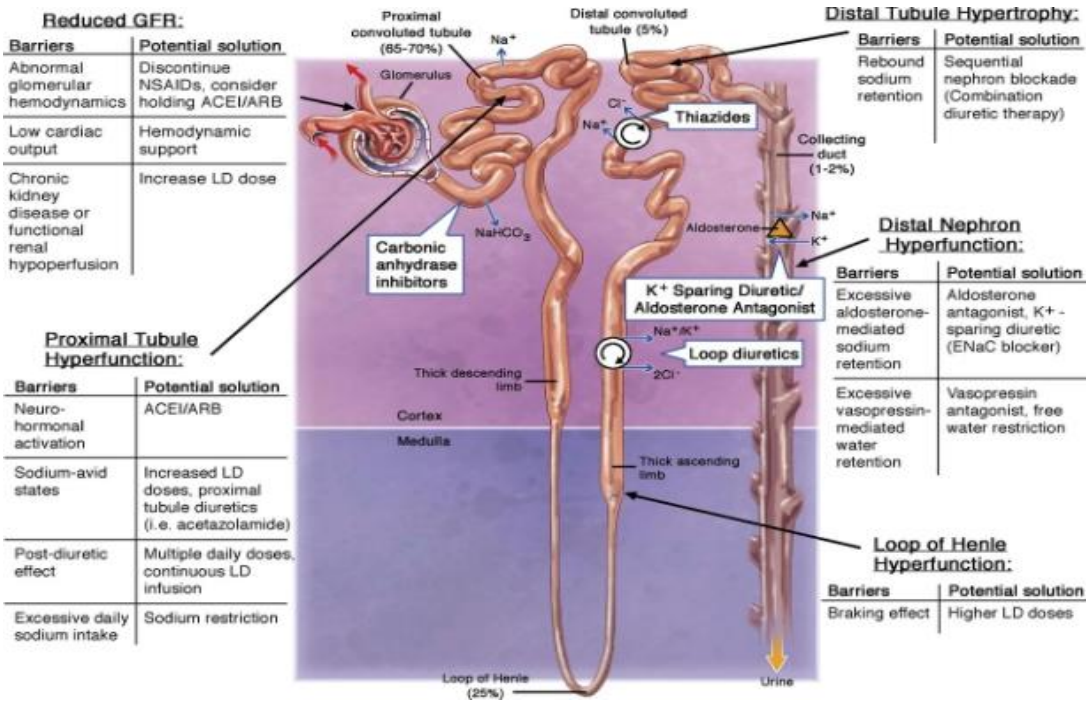

Fig. 1: Diuretic Therapy

Diuretic drugs are widely used for the treatment of patients with edema. Among these drugs , loop diuretics such as furosemide and perhaps the most frequently prescribed, and their clinical pharmacology is better than is that of other diuretics. These review will therefore focus on this class of diuretics, but others will be discussed as well. Clinical pharmacology of diuretics pharmacokinetics . the pharmacologic characteristics of all loop diuretics are similar. Therefore a lack of response to adequate doses of one loop diuretic (7).

Drugs used in treatment of diuretics

1] Furosemide

Furosemide Indications

The food and drug administration (FDA) has approved the use of furosemide in the treatment of conditions with volume overload and edema secondary and congestive heart failure exacerbation liver failure , or renal failure including the nephrotic syndrome

Patients with acutely decompensated heart failure (ADHF) with volume overload who have not received diuretics previously, the initial dose of furosemide should be 20 to 40 mg intravenously, and later , titrate the furosemide dose according to the clinical response of patients . However those patients with ADHF with a normal kidney function who are on chronic diuretic therapy, the initial dose of furosemide can be initiated as an equivalent to or greater than the total oral maintenance dose of furosemide patients takes daily. Subsequently the diuretic dose is adjusted according to the clinical response of the patient. Never the less, the starting with higher doses of furosemide , that is , at a dose of 2.5 times the total daily oral dose of furosemide per day , has shown a significant trend toward a rapid improvement in the global assessment of patients symptoms (8).

Furosemide sold under the brand name lasixamong others, is a medication used to treat fluid build up due to heart failure, liver scarring , or kidney disease . it may also be used for treatment of high blood pressure. It can be taken by injection into vein or by mouth. When taken by mouth, it typically begins working with an hour, while intravenously, it typically begins working within five minutes (9).

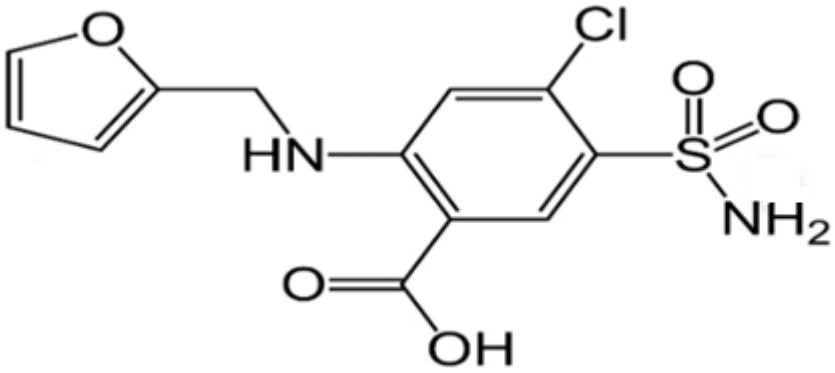

Fig.2: Structure of Furosemide

The time course of delivery of furosemide into urine an independent determinant of overall response after an oral or intravenous dose of Furosemide, there is considerable interindividual variability in the amount of uncharged drug delivered into the urine. On average approximately half as much reaches the intraurinal site of action with an oral compared to an

intravenous dose . However , the natriuretic response to the same dose administered by either route is virtually the same . Similarly after pretreatment with probenecid the same total amount (12)

Pharmacokinetic

Molecular weight (Daltons) 330.7

% Bioavailability 47 – 70 %

Bioavailability with end stage renal disease 43- 46 %

% protein binding 91 – 99 (15)

Volume of distribution (L/Kg) 0.07 – 0.2 (16)

Volume of distribution may be higher in patients with cirrhosis of nephrotic syndrome

Excretion

% excreted in urine (% of total dose) 60- 90

% excreted unchanged in urine (% of total dose) 53.1 – 58.8

% excreted in feces (% of total dose) 7 – 9

% excreted in bile (% of total dose) 6-9

Approximately 10% is metabolized by the liver in healthy individuals, but this percentage may be greater in individuals with severe renal failure

Renal clearance (ml / min/kg) 2.0 (15)

Elimination half life (hrs) 2

Prolonged in congestive heart failure (mean 3.4 hrs) (16)

Prolonged in severe renal failure (4-6 hrs) and anephric patients (1.5- 9)

Time to peak concentration (hrs)

Intravenous administration 0.3

Oral solution 0.83 (15)

Oral tablet 1.45

The pharmacokinetics of furesemide are apparently not significantly altered by food

No direct relationship has been found between furosemide concentration in the plasma and furosemide efficacy . Efficacy depends upon the concentration of furosemide in urine (14)

Name

Furosemide is the IIN and BAN (17) . the previous BAN was furosemide

Some of the brand names under which furosemide is marketed include :- Aisemide, Apofurosemide , Beronald, Desdemine, Discoid , Diural, Diurapid , Dryptal, Durafurid , Edemid, Errolon , Eutensin , Flusapex ,Frudix , frusetic , Frusid , Fulsix , Fuluvamide , Furesis , Furix , Furo-puren , Furon,Furosedon , fusid frusone, hydro –rapid, impugan ,katlex , profemin ,rosemide , rusyde , salix, uremide ,and urex

Furosemide disposition in cirrhotic patients

Frurosemide disposition in 7 cirrhotic subjects and 4 age matched healthy controls was studied to determine the contribution of differences in pharmacokinetics to the decreased responsiveness observed in cirrhotics . subjects were given 80 mg of furosemide orally and intravenously on

separate occasions ,and plasma and urine samples were collected and analysed for furosemide by high performance liquid chromatography . the half life of furosemide was 74% greater in cirrhotic subjects (13)

Diuretics use in autism

A drug normally used to increase the rate at which peopleurinate improves some of the symptoms of austim in children, according to small clinical trial published today in translational Psychiatry46. Austim is a neuro development disorder characterized by impaired Communication and social interaction and also by repetitive behaviors in those affected.Research has shown that signaling by a molecule called GABA , a neurotransmitter which normally dampens down neuronal activity , is altered in austim . And that this disruption of GABA , a neurotransmitter which normally dampens down neuronal activity , is alteredin autism . and that this disruption of GABA is due to increased levels of chgloride ions in the brain cells . reducing these chloride ions levels might help to treat the condition, hypothesized Yehezel Ben –ari , a neuroscientist at the Mediterranean Institute of Neurobiology. In 2010 , Ben-Ari and his co-author reported that a three –month course of bumetanide – a diuretic that lowers the concentration of chloride ions by blocking the entry of ions into the cell – decreased autistic behavior in five infants without causing side effects (10)

When individual present with fluid imbalance (depletion) due to diurectics , adverse events such as :

Dry mouth , Thirst, Weakness, Lethargy, Drowsiness, Restlessness, Muscle pain or cramps, Confusion, Seizures, Muscular fatigue, Hypotension, Oliguria (decrease or absent production of urine), Tachycardia, Gastrointestinal disturbances may occur (11)

Examples of Diuretics

Thiazide diuretics :

Chlorothiazide (diuril)

Chlorthalidone (Hygroton)

Indapamide (lozol)

Hydrochlorothizide (Hydrodiuril)

Methylclothiazide (Enduron)

Metolazone (Zaroxolyn)

Loop diuretics :-

Bumetanide (Edecrine)

Furosemide (Lasix)

Ethacrinate (Edecrin)

Torsemide (Demadex)

Potassium sparing diuretics :-

Amiloride hydrochloride

Spironolactone (Aldactone)

Triamterene (Dyrenium)

CONCLUSION:

Hypertension is a complex disease. If looked at from a molecular perspective it is a phenotype (elevated blood pressure) that results from alterations in the multiple pathways of blood pressure regulation. As such, determining the likely efficacy of different therapies for hypertension is challenging. However, a large number of candidate genes and single-nucleotide polymorphisms for both disease etiology and response to therapies have already been identified. There is a great need for these to be replicated in studies with sufficient size and power.

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