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Diuretics are defined as substances that increase the amount of urinary sodium and subsequently that of water. They are widely used in cardiovascular medicine and currently recommended as one of the treatment options for uncomplicated hypertension, hypertension accompanied by congestive heart failure and obligatory in all forms of congestive heart failure and renal insufficiency. Diuretics currently used in cardiovascular medicine act mainly at four different sites: (i) Proximal tubule (Carbonic anhydrase inhibitors), (ii) Loop of Henle (loop diuretics), (iii) Distal tubule (Thiazide etc) and (iv) Collecting tubule (potassium sparing diuretics) (Reyes and Taylor, 1999).

When a diuretic drug is administered, rates of urinary sodium and chloride excretion usually increase above baseline leading to a period of negative sodium and chloride balance. This natriuresis and chloriuresis is the hallmark of effective therapy. Yet, within several days to weeks, net daily solute and water losses decline and eventually approach pre diuretic levels, despite continuous drug administration. These changes in diuretic responsiveness result from adaptive processes that occur during diuretic therapy. When these processes become manifest, once the desired extracellular fluid (ECF) volume has been attained, they are clinically useful and prevent progressive ECF volume contraction. When these processes develop prior to achieving the desired ECF volume, they can be viewed as contributing to diuretic resistance (Ellison, 1999). An edematous patient may be deemed resistant to diuretic if treatment with a potent diuretic drug in therapeutic doses fails to reduce extra cellular fluid (ECF) (Ellison, 1991). Diuretic resistance may result from dietary indiscretion, poor compliance, impaired bioavailability, impaired diuretic secretion into lumen of renal tubule or because other drugs interfere with diuretic activity.

Resistance to loop diuretics is a common clinical phenomenon and the resistance to natriuretic response to furosemide is well documented.
Mechanism for diuretic resistance may be divided into two types, pharmacokinetic and pharmacodynamic mechanism (Brater, 1994). The pharmacokinetic determinant of renal response to diuretic are a function of both total amount of free diuretic reaching the site of action and the diuretics time course of delivery into urine which may be changed because of alteration in volume of distribution, bioavailability or protein binding in edematous disorders. The pharmacodynamic determinants of renal response are poorly elucidated. Diuretic resistance results from diuretic adaptations, which can be classified as those that occur during diuretic action, those that cause sodium retention in the short term (causing post diuretic NaCl retention) and those that increase sodium retention chronically i.e. Braking phenomena (Ellison, 1999).

Chronic administration of loop diuretic lead to progressive diminishing response (Wilcox et al., 1983). Increased sodium reabsorption due to hypertrophy and hyperplasia of epithelial cells of distal tubule attenuates the effectiveness of loop diuretic (Kaissling et al., 1985; Kaissling et al., 1988; Loon et al., 1989). Another pharmacodynamic alteration is change in the sensitivity of renal tubular cells to diuretic through neurohumoral factors activated in the edematous disorder (Kelly et al., 1983; Peterson et al., 1991; Almeshari et al., 1993).

Common clinical conditions where diuretic resistance is most frequently encountered are congestive heart failure, chronic renal insufficiency, nephrotic syndrome and cirrhosis. The generation of diuretic resistance in these clinical condition most of the time, has both pharmacokinetic and pharmacodynamic component. Understanding the mechanisms of diuretic action and adaptation, the causes of diuretic resistance and goals of diuretic treatment helps one to select an optimal approach to the diuretic resistant patient.
There are several modifications of traditional diuretic usage, which have been effective in overcoming diuretic resistance:

1. High doses of loop diuretics are frequently employed to treat severe volume overload, especially when treatment is urgent. Hypokalemia, hyponatremia, hypomagnesemia and hypotension frequently result because of excessive fluid and electrolyte losses. Irreversible toxicity and thymine deficiency are other potential risk factors associated with high doses of loop diuretics.

2. Administration of more than one class of diuretic. Addition of distal convoluted tubule diuretic impairs post diuretic sodium retention and blocks distal tubular reabsorption of sodium during chronic loop diuretic administration. Synergistic response is seen when hydrochlorothiazide is administered with furosemide (sequential nephron blockade) in patients with refractory congestive heart failure, nephrotic syndrome and azotemia (Wollam et al., 1982; Loon et al., 1989; Dormans and Gerlag, 1996). Reabsorption of sodium at collecting duct, play a smaller but significant role. Addition of spironolactone to furosemide increases basal urinary sodium (Na) excretion as compared to furosemide alone in chronic therapy. When loop diuretic increases, the luminal Na in the cortical duct Na absorption increases only modestly unless circulating aldosterone levels are increased at same time. As might be predicted addition of collecting tubule diuretic should be most effective when Na retention is generated primarily by elevated circulating aldosterone (Kaispling et al., 1988).

3. Constant intravenous infusion of loop diuretic or using a modified (slow) release preparation may lead to higher efficiency, delay and blunting of the development of resistance.

4. Ultrafiltration: The potential benefit of mechanical ultra filtration over medical diuresis is it involves modest stimulation of the renin/angiotensin/aldosterone axis and does not activate macula densa.
Thus the combination of low dose of diuretics with different sites of action in the kidney, appear rationale rather than conventional high dose monotherapy to which patients are poorly responsive or unresponsive. However, most of these combination studies are done with patients with edematous disorder. The present study has been designed to evaluate the effect of chronic dosing of hydrochlorothiazide (50mg) plus furosemide (40mg) and spironolactone (50mg) plus furosemide (40mg) in comparison to furosemide (40mg), furosemide (80 mg), hydrochlorothiazide (50 mg), spironolactone (50 mg) and placebo on electrolytes, urine volume, body weight and arterial blood pressure in healthy human subjects.