University of Basrah

Collage of pharmacy

Department of clinical pharmacy

جامعة البصرة

كلية الصيدلة

# Diuretics Resistance

**اعداد الطالبة ضحى زيدون عبد الحميد**

**و الطالبة عذراء عقيل مسلم**

**بأشراف الدكتور علي محمد هادي**

## Introduction

Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretics.

The causes of diuretics resistance include poor adherence to drug therapy or dietary sodium restriction, pharmacokinetic issues, compensatory increases in sodium reabsorption in nephron sites that are not blocked by the diuretics.

As you know that diuretics use for many conditions like heart failure , chronic hypertension , liver cirrhosis , renal failure all these conditions have same problem , sodium water retention or what we call it edema , fluid retention lead to increase over load on the body organs also increase body weight of patient .

Normally sodium and water regulate by the kidney dependent on arterial volume which constitutes about 1.25% of the total body volume in non-edematous patients expansion of the extracellular fluid.

Volume triggers the kidney to excrete excess sodium and water , while in edematous states such as heart failure the homeostatic mechanism is altered and retention of sodium and water persists , despite extracellular volume expansion in addition the maximum attainable amount of sodium excretion may be reduce in heart failure , lessening the degree of natriuresis , in mild cases of kidney failure and heart failure diuretic resistance not occure, but in moderate and severe cases diuretic resistance more frequently occure and became a clinical problem , this occure due to decrease plasma blood flow and impaired secretion by the proximal tubules , other cause which result in diuretic resistance drug – drug interaction like NSAIDS may alter the renal hemodynamic by decrease renal blood flow through effect on cox1 and cox2.

Loop diuretics are firmly bound to serum proteins, they reach the tubular lumen predominantly by active secretion and not by glomerular filtration or passive diffusion. In renal insufficiency secretion of furosemide and other loop diuretics is reduced because of accumulation of endogenic organic anions competing with loop diuretics for the

receptor sites of the organic anion transporter. Higher doses are required to overcome this competitive inhibition and to obtain therapeutic urinary concentrations. The bioavailability of loop diuretics is unaltered in CHF, but peak urinary concentrations are reduced and tend to occur later, resulting in a less powerful diuretic effect. This is a second pharmacokinetic mechanism that interferes with a satisfactory diuresis.

When a short acting diuretic like furosemide is administered, it will result in natriuresis as long as its concentration in tubular fluid is high enough to block the Na+/K+/2CI cotransporter. When urinary concentrations decline below the diuretic threshold about six hours later, compensatory sodium retention occurs during the rest of the day. This is called post diuretic salt retention. If sodium intake is high, post diuretic salt retention can completely abolish the effect of the diuretic and a negative sodium balance is not achieved. If sodium intake is low, compensatory sodium retention in the post diuretic phase is incomplete and there is a net loss of sodium.

Chronic administration of loop diuretics results in a diminished natriuretic effect (“the braking phenomenon”) Major determinants of this braking phenomenon are functional and structural adaptations that occur in downstream nephron segments. Studies in rats have shown that chronic administration of a loop diuretic induces hypertrophy and hyperplasia in epithelial cells of the distal convoluted tubule, leading to an increased reabsorption of sodium in this segment, thereby blunting the natriuretic effect. These adaptations also occur in humans.

**Aim of our study** is to know how diuretic resistance occurs and how can you resolve or treat this condition.

## ***Patients and methods:***

This study was carried out at Al Basra general hospital in internal medicine wards from February 2018 to May 2018. Twenty four patients were enrolled in this study.

All patients have a certain cause of edema that made diuretics use a prerequisite. So they had a history of using diuretics with different groups however mainly loop diuretics were used .

After you understand the causes of diuretic resistance now you must know how to monitor this case and decrease the resistance.... actually there are many strategies

*pre-diuresis precautions: this point mean must ensure restriction of sodium intake why? Due to increase sodium intake cause refractory edema.... and to regulate level of sodium its simply done by collection of urine of 24 hr and measure sodium concentration that pass in urine if the value more than 100meq per day that mean no sodium restriction ... but if the level less than 100meq per day or very small amount this indicate sodium restriction.

*pre- diuresis lab : this point mean measure serum concentration of albumin , urea , creatinine , Na , Cl , K , Ca , BUN , uric acid ... And other lab investigation to indicate any abnormality after given treatment and if there is response for the given treatment, and prognosis

*pre-diuresis image: like chest x ray, ultrasound for abdomen and pelvis. ECHO, this will need later to follow up the response or to detect side effect of diuretics .

All these methods for monitor the case and follow up of patient because you are responsible for follow up and ensure that there is benefit from your treatment and response.... not include only give a medication only method for decrease the diuretic resistance.

*Restrict salt intake .

*Change dose of given diuretic .

*Change the time and frequency of diuretic .

*Give combination of agents instead of give one agent this help to increase effect and decrease given dose and side effect .

*Give diuretic through Iv route instead of oral route .

*Measure the body weight and other parameter to ensure the effect of the therapy .

*Use different agents with different mechanisms to increase efficacy of diuretics

All these factors were found to help to decrease diuretic resistance.

**Questionnaire for diuretics resistance:**

**Age:** **Gender:** **Occupation:** **BMI:** **Body Wt.**

**B.P:** **Diuretic(s) name:** **Dose(s):**

**Time since diuretic use:**

**PMH:**

**PMNH:**

**Measured parameters:**

| Parameter | Value |
|---|---|
| **S. creatinine** | |
| **S. urea** | |
| **BUN** | |
| **Na** | |
| **K** | |
| **Cl** | |
| **Ca** | |
| **HDL** | |
| **LDL** | |
| **TG** | |
| **CHOL.** | |
| **Fractional Na excretion (FeNa). ٪** | |
| **Spot urinary Na.** | |
| **Urinary Na – K ratio.** | |
| **UOP** | |
| **GFR** | |

## ***Results:***

**1- Serum and urine proteins means in patients using different diuretics (3 months – 3 years).**

| Diuretic dose (Daily) | S. Albumin (g/dl) | Urine protein(mg/dl) |
|---|---|---|
| **20 mg** | 1.8 | 218 |
| **40 mg** | 3.78 | 200 |
| **60 mg** | 4.1 | 100 |
| **80 mg** | 4.5 | 30 |

**2- Serum lipid profile means in patients using different diuretics (3 months – 3 years).**

| Diuretic dose (Daily) | S. Cholesterol (mg/dl) | S. LDL (mg/dl) | S. HDL (mg/dl) | S. TG (mg/dl) |
|---|---|---|---|---|
| **20 mg** | 177 | 43 | 46 | 100 |
| **40 mg** | 182 | 47 | 44 | 110 |
| **60 mg** | 187 | 48 | 40 | 130 |
| **80 mg** | 215 | 50 | 38 | 160 |

**3- Serum electrolytes means in patients using different diuretics (3 months – 3 years).**

| Diuretic dose (Daily) | S. Calcium (mg/dl) | S. Potassium (mmol/dl) | S. Sodium (mmol/dl) | S. Chloride (mg/dl) |
|---|---|---|---|---|
| **20 mg** | 5.12 | 3.45 | 139 | 96 |
| **40 mg** | 6.34 | 4.62 | 144 | 101 |
| **60 mg** | 7.82 | 4.85 | 140 | 107 |
| **80 mg** | 8.01 | 5.07 | 151 | 113 |

**4- Renal function test means in patients using different diuretics (3 months – 3 years).**

| Diuretic dose (Daily) | S. BUN (mg/dl) | S. Urea (mg/dl) | S. Creatinine (mg/dl) |
|---|---|---|---|
| **20 mg** | 37.55 | 121.44 | 4.12 |
| **40 mg** | 44.57 | 135.24 | 4.23 |
| **60 mg** | 61.12 | 143.71 | 5.17 |
| **80 mg** | 88.29 | 169.93 | 6.39 |

## ***Disscution***

Diuretic drugs are used almost universally in patient with congestive heart failure , most frequently the potent loop diuretic , despite their un proven effect on survival ,their indisputable efficacy in relieving congestive symptoms make them first line therapy for most patient . In the treatment of more advance stages of heart failure diuretics may fail to control salt and water retention despite the use of appropriate doses.

Diuretic resistance may be caused by decrease renal function and reduce and delayed peak concentration of loop diuretics in the tubular fluid, but it can also be observed in the absence of these pharmacokinetics abnormalities. When effect of a short acting diuretic has worn off, post diuretic salt retention will occurs during the rest of the day. chronic treatment with loop diuretic result in compensatory hypertrophy of epithelial cells downstream from the thick ascending limb and consequently its diuretic effect will be blunted .strategies to overcome diuretic resistance include restriction of sodium intake , change dose , change time of administration , combination diuretics therapy.

First we must know how edema or fluid retention occurs? as you know that any injury or damage lead to fluid electrolyte imbalance lead to activate sympathetic system in the body end with activation of rennin – angiotensin system lead to formation of aldosterone which cause sodium water retention . this pathway occurs heart and renal fail to obtain adequate fluid to the body requirement so here action of compensatory mechanism appear and cause abnormal fluid and electrolyte retention .and incase of prolong effect of compensatory mechanism result in remodeling in the organs include heart or kidney .

Use of diuretics in order to relieving the symptoms of heart failure but not treat the remodeling that occurs , remodeling could be treat by ACI inhibitors and beta blocker … know we must talk about factors that

enhance development of refractory edema and decrease response to usual diuretic regimen

*First factor is high salt intake which prevents net fluid loss even adequate therapeutic doses of diuretics.

*Second factor that may contribute to refractory edema is decrease loop diuretic secretion. An important step in the mechanism of action of loop diuretics is that they enter the tubular lumen by secretion in the proximal tubules, not by glomerular filtration. After that loop diuretic inhibit the Na/K/2cl carrier in the luminal membrane of the thick ascending limb of loop of henle, which will reduce NaCl reabsorption.

Diuretics efficacy is mainly related to urinary excretion rate of the drug, rather than to its plasma concentration. in case of CHF renal perfusion and tubular blood supply is decrease due to decrease cardiac output , which decrease the delivery of diuretic to their site of action cause in significant effect . It is also well known that loop diuretics are highly > or = 95% protein bound, which keep the diuretic within intra vascular space, which will ensure good delivery of diuretic to the kidney.

Hypoalbuminemia may occur in CHF if albumin is filtered in the urine secondary to high venous pressure. Secondary to hypoalbuminemia the degree of diuretic – protein binding is reduce , which will result in larger extravascular space of distribution of the diuretic with slow rate of delivery to the kidney and then reduce diuresis . In addition the filtered albumin in the urine secondary to high venous pressure may bind loop diuretic in the tubular lumen and interfere with its action

*The third and one of important causes of diuretics resistance is the use of NSAI drugs which reduce the synthesis of prostaglandin which will affect the diuretic responsiveness

*The forth factor is that some patient with DR have decrease naturisis despite adequate urinary delivery of diuretics.

This problem is often doing to increase tubular sodium reabsorption in nephron segments other than the loop of henle with the chronic of diuretics (the diuretics braking phenomena). Increase tubular sodium reabsorption associate with diuretics braking phenomena may occurs at different segments of nephron (proximal tubules due to angiotensin system, collect tubules due to mineralocorticoid activity).

*Fifth factor include inadequate diuretic dose or frequency (decrease patient compliances).

*Final and most important one in CHF patient may decrease intestinal perfusion lead to reduce intestinal motility and intestinal mucosal edema lead to decrease diuretic absorption.

# References:


1. The burden of acute heart failure on U.S. emergency departments. JACC Heart fail. 2014;2(3):269–77. Epub 2014/06/24.
2. Collins SP, Jenkins CA, Harrell Jr FE, Liu D, Miller KF, Lindsell CJ, et al. Identification of emergency department patients with acute heart failure at low risk for 30-day adverse events: the STRATIFY decision tool. JACC Heart fail. 2015;3(10):737–47. Epub 2015/10/10.
3. Adams Jr KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209–16. Epub 2005/04/23.
4. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. Engl J Med. 2011;364(9):797–805. Epub 2011/03/04.
5. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. Nat Rev Cardiol. 2015;12(3):184–92.
6. Packer M, Cohn JN, Abraham WT. Consensus recommendations for the management of chronic heart failure. Am J Cardiol. 1999;83:1A-38.
7. Wilcox CS. Diuretics. In Brenner BM, Recter FC,eds. The Kidney. Philadelphia: WB Sauders, 1996:2299-330.
8. Neuberg GW, Miller AB,O`Connor CM, et al. Diuretic resistance predict mortality in patient with advanced heart failure. Am Heart J. 2002;144:31-8.
9. Ellison DH. Diuretic resistance : physiology and therapeutics. Semin Nephrol. 1999;19:581-97.
10. Kaislling B, Stanton BA. Adaptation of distal tubule and collecting duct to increased sodium delivery. 1. Ultrastructure. Am J Physiol.1998;255:F1256-68.
11. Kaislling B, Stanton BA. Adaptation of distal tubule and collecting duct to increased sodium delivery. II. Sodium and potassium transport. Am J Physiol.1998;255:F1269-75.
12. Loon NR, Wilcox CS, Unwin RJ. Mechanism of impaired natriuretic response to furosemide during prolonged therapy. Kidney Int. 1989;36:682-9.