Mechanism of action of diuretics in edema syndrome and ascites in cancer patients

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Abstract- **Diuretics are a widely used class of medications in the treatment of cardiovascular diseases such as arterial hypertension, among others. They also play a role in the treatment of various other conditions.**
In addition to their use in cardiovascular diseases, they find significant application in treating conditions such as edema and ascites, particularly in oncological settings. In patients with edema caused by oncological diseases, especially those in terminal stages, and in patients with edema syndrome and ascites, diuretics can be beneficial in certain cases, assisting oncologists in their management.
Their application follows specific guidelines due to the fact that different diuretics operate through distinct mechanisms of action. Although closely related in the emergence of conditions, edema syndrome and ascites exhibit different behaviors in the body. Therefore, their treatment must be tailored to the mechanism of action of different diuretics in cancer patients. This article aims to summarize the various mechanisms to guide proper management in oncology patients.

Keywords: **diuretics, ascites, mechanism of action, oncological disease, edema.**

Introduction

Ascites is a medical condition characterized by the accumulation of fluid in the abdominal cavity, often associated with liver cirrhosis, heart failure, or other underlying diseases. Diuretics play a crucial role in managing ascites by promoting the excretion of excess fluid from the body through increased urine production. These medications, such as loop diuretics like furosemide and thiazide diuretics like spironolactone, help reduce fluid retention, alleviate symptoms, and improve the overall well-being of individuals with ascites. However, careful monitoring and individualized dosing are essential to balance the benefits and potential risks associated with diuretic therapy in this context [1,2].

The volume and composition of the excess fluid in the body remain constant, sustained through numerous mechanisms. A defined relationship exists between the intake of sodium in the body and its excretion in the urine. For instance, if the human body ingests 5 grams of sodium chloride or 210 mmol daily, an equivalent amount is excreted in the urine. This equilibrium ensures the stability of both the external fluid volume and, consequently, the internal fluid volume. The kidneys play a pivotal role in maintaining this balance [1,2,3].

Approximately 21,000 mmol/d of sodium chloride undergo filtration in the glomeruli of the kidneys, equivalent to around 150 mmol/l (sodium chloride x 140 l/d) in glomerular filtration within the kidneys.

Out of the sodium chloride filtered in the glomeruli, 99% is reabsorbed in the renal tubules, with only one percent being excreted in the urine. The mechanisms ensuring individual volume constancy are highly sensitive to the amount of sodium chloride introduced into the body through food, prompting the kidneys to increase sodium excretion in response to the load.

In evaluative states of the organism, regardless of the triggering factor, the kidneys maintain a high level of sodium reabsorption, approaching 100% of the filtering charge magnitude. This robust sodium reabsorption is a consequence of overarching mechanisms that can involve higher degrees of initial units in hemodynamic disruptions, while the sympathetic-adrenal and hormonal systems of the adrenal glands play a more prominent role in the executive unit, limiting the amount of sodium excreted in the urine.

Under normal sodium intake levels, urine excretion decreases, resulting in a negative sodium balance, increased non-specific fluid volume, and the onset of edema. In patients with edema, renal sodium excretion typically does not increase as significantly in response to increased dietary intake as in healthy individuals [3,4].

Theoretically, fluid retention can occur not only with decreased sodium excretion by the kidneys but also with abnormally high salt and water intake. Large amounts of salts and water administered parenterally can induce edema, but this usually resolves rapidly if kidney function is normal. The factor influencing opening formation has limited temporal importance, as the initial maintenance of sodium excretion from the body holds universal significance in the

pathogenic connection of the opening. Throughout evolution, the organism has developed systems to store sodium reserves. A decrease in circulatory blood volume triggers an antinatriuretic reaction in the kidneys.

Blood loss leads to the retention of sodium excretion through the kidneys. The elevated sodium concentration reflexively increases the release of antidiuretic hormone from the posterior part of the pituitary gland, thereby ensuring the body retains a sufficient amount of sodium and water to restore the liquid portion of the blood lost due to blood loss [3,4,5].

Evidently, these homeostatic reactions play a crucial role in maintaining circulatory blood volume in cases of extreme blood loss and form the foundation of the edema syndrome. This mechanism is also applicable in cancer patients.

These reactions arise from hemodynamic disturbances; the homeostasis system responds by preserving the excretion of sodium and water from the body, despite the disrupted hemodynamics. In cases where there is no basis for blood loss but an accumulation of sodium and water occurs in the interstitial space of the body, edema syndrome ensues.

Various forms of edema typically present three main conditions: heart failure, cirrhosis of the liver with the development of ascites, and nephrotic syndrome. In the case of nephrotic syndrome, not only is there an increase in the volume of excess fluid, but there are also disruptions in Starling's forces, which normally distribute fluid between the capillary wall, causing a disturbance in fluid distribution between the intravascular and interstitial spaces [5].

Several factors can influence the capillary walls, including:

1.Perfusion pressure in the capillaries, facilitating the transfer of water and salts into the interstitial space.

2.Oncotic pressure of protein plasma, maintaining water in the vascular bed.

3.Pressure in the interspecific space.

4.Movement of lymphatic fluid.

5.Disruption of vascular wall permeability caused by the pathological process, which can also contribute to the development of edema.

In heart failure for example, there is an observed increase in capillary hydrostatic pressure, leading to an augmented transition of fluid from the intravascular space and a subsequent decrease in the volume of circulatory blood. In nephrotic syndrome and cirrhosis of the liver, hypoalbuminemia is present, causing a reduction in the oncotic pressure of the blood. This results in the movement of fluids from the bloodstream into the interstitial space. In such scenarios, the primary decrease in the total circulating blood serves as a stimulus for the onset of a sodium and water retention reaction [4,5,6].

While this explanation is schematic, it helps elucidate the mechanism underlying edema and the action of physiological mechanisms that regulate volume under pathological conditions. It's important to note that, despite the presented facts, various mechanisms cannot fully account for the proposed variations in the outflow syndrome in these diseases.

The typical sodium retention response, leading to water retention, implies the development of hypernatremia and an increase in blood osmotic pressure. This, in turn, triggers the osmoreceptor systems' response and a reflexive increase in antidiuretic hormone secretion. In some cases of this reaction, when water retention is predominantly tied to sodium retention, hypoosmolarity and hyponatremia may occur. However, in the majority of cases, the extracellular fluid maintains isoosmotic levels in the blood plasma, and this doesn't result in a significant increase in antidiuretic hormone in the blood [2,3,6].

This is because, in edema, the primary importance of sodium retention and secondary water retention is limited.

The mechanisms behind the kidneys significantly increasing the reabsorption of sodium in the outflow syndrome are not fully understood. Broadly speaking, the prevailing concepts suggest that when the circulation is under threat, there is an augmented reabsorption of sodium and water from the kidney tubules. This doesn't disrupt the kidney's overall function but rather activates a particularly residual regulatory mechanism that operates both under normal conditions and in pathology. Exploring these possibilities, an extraordinary increase in the extracellular space triggers this action, as long as there is an increased transudation from blood plasma or a threat to circulation. However, these mechanisms governing sodium reabsorption have not been thoroughly studied.

The traditional explanation for edema development involves a reduction in the effectiveness of the effective arterial volume. This occurs due to the movement of liquid from the intravascular space into the extravascular space under the influence of Starling forces. This fluid transition may result from increased venous pressure in heart failure or reduced oncotic pressure of the blood due to protein loss in nephrotic syndrome. Regardless of the primary cause, triggering fluid movement from the vascular space to the interstitial space activates a series of homeostatic mechanisms aimed at eliminating sodium water retention in the body [4,5,6].

A potential trigger for homeostatic reactions could be a discrepancy between the vascular bed and the volume of circulating blood, prompting a homeostatic response.

Undoubtedly, a key factor is an increase in the function of the sympathetic-adrenal system. This increase, operating through several mechanisms, induces a sodium response in the kidney tubules. The initial mechanism involves a decrease in glomerular filtration, automatically leading to an increased fractional reabsorption of sodium.

The second mechanism involves a reduction in medullary blood flow due to vasoconstriction in the kidney vessels induced by sympathomimetic amines.

The third mechanism encompasses the activation of the renin-angiotensin systems, leading to increased sodium absorption through the renal formation of angiotensin 2. This substance, in turn, stimulates renal tubular sodium reabsorption by activating aldosterone synthesis from the adrenal cortex, subsequently promoting sodium reabsorption [7].

Quaternary sympathomimetic amines, generated in the kidneys through beta-adrenomimetic effects, significantly enhance sodium reabsorption. For instance, beta-adrenoblockers notably increase sodium excretion by reducing tubular reabsorption of this ion in rats with chronic circulatory failure.

Chronic circulatory insufficiency evidently heightens the adrenergic nerve tone in the kidneys, resulting in sodium retention. This is why the administration of beta blockers reduces sodium transport in the kidney tubules. Other factors influencing sodium retention and release in the body include a decrease in the activity of natriuretic factors in the blood, a reduction in medullary blood flow in the kidneys, and an increased sensitivity of the kidneys to endogenous antibiotic hormones, among other factors.

Diuretics act by blocking renal tubular sodium reabsorption, typically with therapeutic intent. They are sufficiently effective in reducing renal tubular sodium reabsorption, leading to an increase in renal sodium excretion surpassing sodium intake. This reduction in body sodium content subsequently results in a decrease in extracellular volume, contributing to the reduction of edema.

Despite emerging theories regarding the mechanism of action of diuretics, particularly their role in primarily expanding the chlorine compartment and blocking its active transport in the loop of Henle, it is crucial to emphasize that the release of sodium remains the pivotal aspect. Sodium, being the primary ion in plasma with the ability to bind a significant amount of water molecules, holds paramount importance in removing the underlying cause of edema by excretion in urine. In the therapy of edema syndrome, it is not only the primary effect that matters but also the secondary effect involving the subsequent loss of sodium ions for chlorine [3,5,7]

It is essential to note that when administering diuretics for edema syndrome, it should coincide with a diet low in sodium. The therapeutic effect of diuretics is complemented by a diet that restricts sodium intake, ensuring a comprehensive approach to managing edema.

Choice of Diuretic

When selecting a diuretic, consideration must be given to its type, which, except for emergency situations, often leads to the use of moderately effective diuretics. Thiazides, in particular, are commonly employed as they generally provide sufficient diuretic effects and are often the initial choice for treating edematous conditions. In such cases, daily prescription is typically unnecessary. Administering thiazides every other day or for an extended period proves effective therapeutically and helps prevent the development of side effects.

The mechanism through which diuretics directly restore electrolyte balance in patients with edema is intricate and not fully comprehended. The compensatory reactions during diuretic therapy result in the release of a significant amount of extracellular fluid from the body. This not only resolves edema but also enhances cardiac function, leading to secondary improvements in hemodynamics. These benefits complement the primary natriuretic mode of action. Thiazide diuretics can be used in conjunction with potassium-sparing diuretics to counteract kaliuresis and prevent hypokalemia.

If thiazide diuretics are prescribed to patients without edema syndrome, moderate hypokalemia may develop (3.2 to 3.9 mmol/l). However, the overall body potassium content is only slightly reduced, and a true deficiency is usually not observed. Patients with secondary aldosteronism on a low-sodium diet are more likely to experience significant potassium deficiency when transitioning to diuretic therapy.

Therefore, it is essential to assess each patient for the potential of hypokalemia. Addressing potassium losses through supplementation or employing potassium-sparing diuretics is a goal that should be considered not only in patients with hypertensive disease but also in those with edema. It's worth noting that even in patients with hypertensive disease, hypokalemia does not typically reach high levels [8].

The most effective approach is the incorporation of a diet rich in potassium and the use of potassium chloride in low-concentration solutions. It is worth noting that organic potassium compounds (citrate, gluconate, orotate, asparaginate) contain a limited amount of potassium and are insufficient replacements in the case of loss.

Resistance

The issue of resistance to diuretic action during prolonged usage poses a significant challenge, necessitating consideration of how to address it.

Continuous diuretic use allows patients to maintain a state free of fluid accumulation for an extended period. However, over time, the diuretic effect may diminish, leading to refractoriness to diuretic action.

Refractoriness can result from disease progression or electrolyte exchange disorders leading to hypovolemia. It is crucial to recognize that the initial response to diuretics is typically the most pronounced. With long-term use, this response diminishes, likely due to a reduction in circulating blood volume.

Refractoriness can also arise from compensatory reactions in the body, such as increased activity of the sympathetic-adrenal system. In individuals with diminished renal function, reduced delivery of an adequate diuretic amount to renal tubules may occur due to decreased calcium secretion [9,10].

Some diuretics, including furosemide, triamterene, and amiloride, act on the luminal surface. Reduction in glomerular filtration and tubular secretion of diuretics disrupts renal function, potentially leading to refractoriness. This is because the concentration of these substances in tubular fluids located in the loop of Henle and the distal part of the nephron decreases. Additionally, decreased glomerular filtration creates conditions for more intensive sodium reabsorption in the proximal tubules and decreased sodium delivery to the loop of Henle, resulting in more complete absorption in the distal nephron segments.

When refractoriness occurs, adjusting the diuretic dosage or introducing other pharmacological agents becomes necessary. For instance, if the maximum natriuretic effect is not achieved with a daily hydrochlorothiazide dose of 100 mg, discontinuing thiazide diuretics and transitioning to loop diuretics like furosemide or ethacrynic acid in doses of 40 and 50 mg, respectively, may be advisable. Concurrent use of thiazides and loop diuretics is discouraged to avoid side effects and the development of refractoriness to loop diuretics, which may require progressively increasing doses, as evidenced by data suggesting increased furosemide doses up to several hundred milligrams per day enhance its effect [7,11].

Very rarely, patients with edema syndrome may develop refractoriness to loop diuretics. In such cases, introducing diuretics with a similar mode of action alongside loop diuretics becomes necessary. Refractoriness in this scenario may be associated with a sharp increase in the reabsorption of the primary filtration in the proximal tubules. Combining the action of loop diuretics with acetazolamide, euphylline, or other xanthine diuretics may be effective.

Acetazolamide and euphylline selectively block proximal sodium reabsorption, increasing the load on the loop of Henle without reabsorption in the proximal ion channels. Simultaneous administration of furosemide can have a significant effect in refractory conditions.

Complementary measures to improve hemodynamics include the introduction of dopamine and dobutamine, agents that enhance cardiac output and renal blood flow, reduce refractoriness, and augment diuretic effectiveness [7,8,9,11].

Another strategy to address refractoriness involves the use of long-acting nitrates and vasodilators like hydralazine. In conditions of heart failure, these substances increase cardiac output, potentially restoring the effectiveness of diuretics. Correcting water-electrolyte imbalances in diuretics or hypoalbuminemic conditions, such as in nephrotic syndrome, can be achieved by administering a solution containing albumin. This also restores sensitivity to diuretics. It's crucial that the albumin solution contains minimal sodium chloride.

In the treatment of edema syndrome, side effects of diuretics are possible. Alongside specific effects described for each diuretic, general side effects such as hypovolemia, hypokalemia, hyperuricemia, and metabolic alkalosis may occur. Hypovolemia results from the rapid loss of significant amounts of sodium and water under high diuretic doses.

Care must be taken not to exceed a reduction in body mass of more than one or two kilograms per day, equivalent to the corresponding urinary fluid loss. Patients with ascites are particularly at risk for increased fluid loss, potentially leading to hypovolemia, which, coupled with liver decompensation, may contribute to hepatic encephalopathy.

The potential development of hyponatremia, believed to be a consequence of excess water retention in the body, results in diluted sodium concentration. The physiological mechanism behind this appears to be the kidney's inability to excrete an adequate amount of dilute urine, leading to a decrease in the clearance of osmotic free water due to increased delivery of non-reabsorbable sodium to the cortical department under the influence of the diuretic. This overload reduces the formation of hypotonic urine, retaining fluids in the body. Reduced water consumption is only likely in cases with a significant correction of water exchange disorders, as thirst is hindered by the limited water that can be ingested [12].

Alkalosis resulting from the action of loop diuretics is due to the loss of chlorine ions. This condition can be corrected by prescribing ammonium chloride. The pathogenesis also involves the significant loss of potassium salts, as substantial potassium loss diminishes alkalosis.

It's essential to note that the occurrence of alkalosis depends not only on the type of diuretic but also on the body's water-salt exchange status and the amount of aldosterone secretion from the adrenal gland's tough layer. There is no complete correlation between the degree of hypokalemia and the potassium balance in the body. The loss of potassium or the use of potassium-sparing diuretics should be approached on an individual basis.

Monitoring potassium loss is crucial in patients receiving cardiac glycosides, especially digitalis glycosides, as hypokalemia increases their toxicity. Additionally, hypokalemia can complicate hepatic encephalopathy in patients with cirrhosis of the liver by stimulating renal ammonogenesis [13].

Hyperuricemia is typically observed during treatment with thiazides (e.g., furosemide and ethacrynic acid). Reduced uric acid secretion due to competition and secretion with diuretics leads to hyperuricemia, with rare occurrences of

gout. Treatment with anti-inflammatory drugs or exacerbation of gout is managed accordingly, and allopurinol is commonly used for complications of hyperuricemia [14].

There is also a possibility of interactions between diuretics and certain medications during the treatment of edema syndrome. A sharp decrease in circulating blood volume can result in orthostatic phenomena when combining diuretics with different mechanisms of action or with hypotensive agents. Temporary relief from side effects in such cases can be achieved by consuming a large amount of sodium chloride.

Particular caution is advised regarding the use of potassium salts in the presence of potassium-sparing diuretics like spironolactone, triamterene, and amiloride. Life-threatening interactions can occur with the simultaneous intake of these medications and potassium salts in cases of renal failure and hypoaldosteronism.

Hypoaldosteronism may be present in diabetes mellitus requiring insulin treatment. The combination of potassium and potassium-sparing diuretics is contraindicated in these diseases. Careful attention is required when using diuretics alongside lithium salts, commonly used in the treatment of manic-depressive psychosis. Diuretics that deprive sodium may stimulate lithium reabsorption, increasing its concentration in the blood. Thiazides and other diuretics should not be used concurrently with lithium salts. Additionally, aminoglycoside antibiotics may enhance ototoxicity when combined with ethacrynic acid. Gentamicin and ethacrynic acid act synergistically, potentially causing side effects in the inner ear. Combining gentamicin with furosemide can intensify its toxic effects on the kidneys [15].

Conclusion

In conclusion, diuretics play a crucial role in managing cancer patients with outflow syndrome and ascites, significantly contributing to improved quality of life. A comprehensive understanding of diuretic mechanisms enables healthcare professionals to make informed decisions tailored to individual patient needs.

The insights discussed here represent only a fraction of our current knowledge about diuretics, with ongoing research continually expanding our understanding. The adaptability of diuretic strategies to individual patient characteristics remains a promising avenue for enhancing treatment outcomes.

Future investigations into specific patterns of response to diuretics in cancer patients are essential. This research holds the potential to refine therapeutic approaches, ensuring more personalized and effective interventions in the care of individuals grappling with the challenges of cancer and associated fluid-related complications. As our understanding advances, the integration of diuretics into cancer care continues to evolve, offering improved outcomes and a better quality of life for patients facing these complex health challenges.

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