oral administration of the non-peptide V_2 antagonist OPC-31260 (5 mg/kg/day) promptly raised the serum sodium level to 134 mEq/l in half a day, followed by the normalization of serum sodium during the rest of the observation period. These changes were closely linked with water diuresis in the hyponatremic rats receiving DDAVP, namely 5 mg/kg OPC-31260 markedly increased urine volume and decreased Uosm. Similarly, the increased expression of AQP-2 mRNA disappeared after administering the non-peptide AVP antagonist. Similar results were obtained in the models of liver cirrhosis and heart failure in which the enhanced AVP secretion plays a role in water retention. The cirrhotic rats were made by the chronic subcutaneous administration of carbon tetrachloride. The non-suppressible secretion of AVP is involved in the impaired water excretion, and OPC-31260 markedly improved water retention in the decompensated state of liver cirrhosis.

Clinical approach to hyponatremia

A clinical trial of OPC-31260 has been undertaken to treat hyponatremia in patients with SIADH and edematous diseases. Intravenous and oral administration of OPC-31260 promptly produced water diuresis in normal volunteers. Also, both single and successive administration of OPC-31260 improved hyponatremia in the patients with SIADH by enhancing water diuresis. We studied whether an acute aquaresis by parenteral administration of OPC-31260 affected hyponatremia in 11 patients with SIADH. A single injection of 0.5 mg/kg OPC-31260 increased the serum sodium level by approximately 3 mEq/l in 4 hours, which was related to a prompt water diuresis, without any change in urinary solute excretion. Several other non-peptide V_2 antagonists have been developed, and they are expected to have therapeutic efficacy in a variety of disorders of water metabolism.

3. Vasopressin Receptor Antagonists

2) Diuretic Therapy

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Key words: thiazide diuretics, loop diuretics, aquaretics

Introduction

Empirical therapies used to treat edema patients in the old days contained what we call "diuretics" today. An excellent example was Guy's Hospital pills. Loop diuretics have been the products of chemical modification of hydrochlorothiazide (hct). Thiazides, the products of chemical modification of sulfonamides, have side effects of polyuria and metabolic acidosis (1).

Saluretics

Thiazide diuretics

The following are the characteristics of thiazide diuretics: 1) Moderate and persistent diuresis lasts about 12 hours (2). A considerable amount of urinary hct excretion persists after 6 hours. Hct concentration in erythrocytes is maintained at 3–16 times as high as that in plasma. 2) Satisfactory diuresis is expected only in those patients whose creatinine clearance (Ccr) exceeds 70 ml/min. 3) Hct acts to counter the enhanced distal tubular sodium reabsorption that limits the natriuresis

induced by the loop diuretics (3). A combination treatment of furosemide (F) – hct is effective against furosemide-resistant edema in congestive heart failure (4), nephrotic syndrome (5), and chronic renal failure (6). Synergistic action is expected in those patients whose Ccr is as low as 16 ml/min. However, potent diuresis is readily accompanied by hyponatremia. Careful adjustment of the hct dosage is mandatory. 4) There is no report of hct potentiating aminoglycoside nephrotoxicity. This may be due either to the relatively small dosage of hct or to the fact that its administration is limited orally.

Loop diuretics

Loop diuretics are the mainstay of diuretic therapy today. 1) Loop diuretics are excreted into the urine either as an unchanged form or as its metabolites (7). The metabolites are increased when plasma F concentration is extremely high (8) or when Ccr of a patient is very low (9). A positive correlation between urinary excretion of unchanged F and urinary excretion of sodium was observed in a patient whose Ccr was about

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K.A. Female 57 Y HCT 100 mg P.O.

Figure 1. The time course of plasma and blood cell (RBC) HCT concentration and cumulative urinary and biliary HCT excretion in patient K.A.

9 ml/min (Fig. 1) (10). This suggests that natriuresis can be expected even in those patients with severe renal dysfunction if F dosage is increased to 300–500 mg/day.

2) Loop diuretics act to counter the Cl^- transport in the thick ascending limb of the loop of Henle. Thus they inhibit the vicious cycle of tubulo-glomerular feedback and prevent oliguria and edema (11). This mechanism of action of loop diuretics might explain their efficacy in patients with low Ccr. 3)

Hyponatremia is more often associated with loop diuretics than with hct. Loop diuretics frequently interact with other drugs. They enhance aminoglycoside nephrotoxicity and ameliorate nonsteroidal antiinflammatory drugs' action.

In summary, diuretics are indispensable for the treatment of edema patients. They are frequently associated with hyponatremia. This is an inevitable consequence of the pharmacological action of saluretics. Arief AJ et al reported neurologi-

Figure 2. Urinary excretion rate-(A) and Uosm-(B) time relationships after administration of six doses of OPC-31260 (●: 3, △: 15, ▲: 30, □: 60, ■: 100, ◆: 200 mg) and placebo (— and dotted lines) on day 2. Data indicate mean $\pm$ S.E.M. for six active-drug subjects (for each dose) or for 12 placebo subjects during fixed periods of urine collection. Statistical comparison with placebo used analysis of variance followed by Dunnett's test for individual comparisons. * $p < 0.05$, ** $p < 0.01$ compared with respective placebo value.

cal manifestations and morbidity of 66 patients with hyponatremia (12). (a) 21 out of 52 patients were diuretic users. (b) Morbidity was as high as 50% in patients with acute hyponatremia. (c) Mortality was 12% in the hyponatremic patients with manifest symptoms. Measures to prevent hyponatremia is warranted, and development of solute free-water diuresis (aquaretics) have long been expected.

Action of aquaretics

Aquaretics antagonize vasopressin in V2 receptors. Nonpeptide V2 antagonists are preferable compared to peptide V2 antagonists. OPC-31260 is a novel, nonpeptide, selective V2 receptor antagonist developed in Japan (13–15). OPC-31260 increases the first 6-hour hypotonic urine volume dose-dependently (Fig. 2) (15). In an early second phase of clinical trial, OPC-31260 30 mg/day was administered to 99 edema patients for 7 days. A significant decrease in urine osmolality and body weight and a significant increase in urine volume were observed. Urinary sodium excretion was not affected. A significant increase in serum Na concentration was observed in patients with hepatic edema. Application of OPC-31260 is expected to expand with the proper adjustment of dosage, and with establishment of the methods of co-administering loop diuretics.

Future of aquaretics

Vasopressin V2 receptor has already been cloned (16, 17). Their mutations have been linked to various types of nephrogenic diabetes insipidus (18). Elucidation of the mechanisms of binding of vasopressin or its antagonists to vasopressin V2 receptors is expected to open the way to further development of aquaretics.

Conclusion

Diuretics will remain a mainstay of treatment for cardiac, renal, or hepatic edema. Here, the treatment of loop diuretic-resistant edema, and the theory, development, and usage of aquaretics were briefly reviewed.

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4. Physiology and Pathophysiology of Acid-Base Homeostasis in the Kidney

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