RECENT ADVANCES IN DIURETIC THERAPY*

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A diuretic which will remove generalized oedema effectively must produce enhanced renal excretion of the predominant extracellular electrolytes (sodium and chloride) with a secondary increase in urine volume. The past few years have seen the development of several groups of very potent oral diuretics. The advantages of a potent oral diuretic are apparent to all oedematous patients.

Carbonic anhydrase inhibitors, e.g. acetazoleamide, by decreasing the exchange of cellular hydrogen ions for tubular fluid sodium, produce a bicarbonate diuresis with a high K : Na ratio. Such action is limited by the lesser availability of body bicarbonate compared with chloride, so that acetazoleamide has a self-limiting diuretic effect and is of little value in moderate to severe oedema. Other disadvantages in the use of carbonic anhydrase inhibitors are a tendency to hypokalaemia and the possibility of renal calcinosis, and hepatic coma in cirrhotics—on prolonged administration.

However, the experience with carbonic anhydrase inhibitors has pioneered the development of associated substituted sulphonamides, the chlorothiazide group. In oral dosage of 1 - 2 g. daily, chlorothiazide is equal or superior in potency to the intramuscular mercurials. The drug is continuously effective and produces a considerable sodium chloride diuresis, with only slight carbonic anhydrase activity, which may lead to hypokalaemia on prolonged administration. Oral potassium supplements are recommended in the periods between chlorothiazide courses.

While chlorothiazide may reduce high blood pressure, *per se*, its action is definite in potentiating the effect of ganglion blocking agents in essential hypertension. This necessitates reduction in the dose of antihypertensives during any prolonged treatment with chlorothiazide.

Attempts to modify the potassium-losing action of the parent compound led to the introduction of hydrochlorothiazide and hydroflumethiazide compounds; these drugs are very potent, but otherwise differ little in their effects.

The chlorothiazides appear to be ideal oral diuretics (potent, rapid acting, continuously effective, and of low toxicity). Patients are rarely unresponsive to chlorothiazide and no electrolyte imbalance occurs with intermittent potassium supplements.

The most effective oral mercurial, while twice as active as acetazoleamide, has only half the potency of parenteral mercury and is somewhat prone to cause gastro-intestinal irritation.

Chlorothiazide and mercurials are additive in their action, since by different action on the same mechanism they block tubular sodium reabsorption. Thus patients, temporarily resistant to mercury, may respond to chlorothiazide and vice versa, and when either alone is ineffective, their use in combination may produce an adequate diuresis.

A feature of generalized oedema is the increased production of aldosterone. This adds further to sodium retention and aggravation of the oedema until the cycle is broken by diuresis or aldosterone antagonism. Amphenone (by inhibiting adrenal secretion), or prednisone (by hypothalmic inhibition or renal tubular competition) decrease the effects of aldosterone. However, the development of synthetic steroid lactones, antagonistic to the action of aldosterone and DOCA on renal tubular cells, offers more promise. The blocking action appears to depend on the amount of mineralocorticoid present, since blockage occurs with greater efficiency in the presence of large doses of DOCA. The steroid lactones are unique diuretics since they cause natri-uresis without kali-uresis, i.e. they block all the renal actions of aldosterone. Spirolactones have had only limited trials in man. The original lactone was active only in large oral doses; however, the recently developed delta-1 and acetylthio derivatives have 10 - 50 times the activity of the parent steroid.

Current therapy with several potent and relatively non-toxic oral diuretics, is a significent advance since Vogl noted 40 years ago that in cases of congestive heart failure, antisyphilitic mercurial treatment produced a diuresis. Since the different types of diuretics act on different mechanisms of ion reabsorption by renal tubules, lack of response to one diuretic now offers the possibility of obtaining a diuresis with other drugs. While several groups of diuretics (carbonic anhydrase inhibitors, amino-uracils, triazines, chlormerodrin) are effective in maintenance therapy and treatment of mild cases of cardiac, renal, and hepatic oedema, only chlorothiazide and mercurials are of value in the initial treatment of moderate to severe oedema.

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