HYDROCHLOROTHIAZIDE & HYDROFLUMETHIAZIDE

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Pitts²⁰ has defined a diuretic as an agent which promotes urinary excretion of sodium and chloride or bicarbonate with secondary loss of water. These ions are, as he points out, the major ones in the extra-cellular fluid, and it may be added that the ideal diuretic would result in excretion of urine (over and above the base line levels) of composition as near as possible to that of this fluid. Rees²⁴ has called this the 'ideal diuretic fluid'.

Since Vogl first noted that a syphilitic patient treated with organic mercurials experienced a diuresis, diuretics of this type have been widely used with great success. However, the poor absorption and the irritant effect of this group of substances on the gastrointestinal tract necessitate the expense and discomfort of parenteral administration. For some years attempts were made to find a potent oral diuretic, but most of these, such as the pure carbonic anhydrase inhibitors, had serious disadvantages. However, in 1957 Novello and Sprague¹⁹ synthesised chlorothiazide (6-chloro-7-sulphamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide), which, in spite of its sulphonamido ($-\text{SO}_2\text{NH}_2$) group seemed to have only a mild inhibitory effect on carbonic anhydrase. By far its most potent action seemed to be an inhibition of sodium and chloride reabsorption in the renal tubules similar to that of the mercurials. However, as might be expected, the presence of the carbonic anhydrase inhibitory effect does result in greater loss of potassium than with mercurials (though this is much less than with the pure carbonic anhydrase inhibitors such as acetazolamide). Clinical trials repeatedly demonstrated that while chlorothiazide was the most satisfactory and safest oral diuretic so far discovered, yet there was a real danger of potassium depletion, especially in cases with severe secondary aldosteronism such as advanced congestive cardiac failure or hepatic cirrhosis, or those on strict sodium restriction.^{1, 16, 23, 26, 27}

In 1958 de Stevens *et al.*³ synthesized dihydrochlorothiazide which only differed from chlorothiazide in having the double bond in the 3:4 position saturated with two hydrogen atoms, and following a pattern now familiar in other fields, a further attempt was made to alter the action of the drug by substituting a trifluoromethyl group for the chlorine atom in position 6 of the hydrochlorothiazide molecule.

Preliminary trials on animals³ suggested that these new derivatives had less inhibitory effect on carbonic anhydrase than the parent substance, and therefore that both potassium and bicarbonate loss were reduced. It was hoped that the problem of hypokalaemia encountered so often in the use of chlorothiazide would be overcome. However, as will be shown, these hopes have not been realised. There is apparently no difference in practice between hydrochlorothiazide and hydroflumethiazide and they will therefore be discussed together.

Mode of Action

As has been stated above, by virtue of its $-\text{SO}_2\text{NH}_2$ group chlorothiazide has some inhibitory effect on carbonic anhydrase. This enzyme catalyses the reaction.

in the renal tubule. Ionisation of H_2CO_3 to H^+ and HCO_3^- makes available hydrogen ions for exchange with cations such as sodium and potassium in the glomerular filtrate, and reabsorption of NaHCO_3 and KHCO_3 results. If the enzyme is inhibited, potassium and bicarbonate as well as sodium will be lost in the urine. This occurs to a large extent with acetazolamide, and much less so with chlorothiazide. With hydrochlorothiazide and hydroflumethiazide this action is still less, but bicarbonate loss is diminished much more than that of potassium. Therefore, the effect of the chlorothiazide group on excretion of this cation

Chlorothiazide

Hydrochlorothiazide

Hydroflumethiazide

cannot wholly be due to inhibition of carbonic anhydrase.

The mercurial-like effect of chlorothiazide and its derivatives on the reabsorption of sodium and chloride has not been elucidated. Pitts²⁰ points out that its action and that of the mercurials is additive, and that they may, therefore, act at different parts of the tubule, or on different mechanisms at the same part. Labelled hydrochlorothiazide has been shown to collect in the distal parts of the proximal convoluted tubules.⁴

Potency, Dosage and Duration of Action

All workers agree that weight for weight hydrochlorothiazide and hydroflumethiazide are 10 to 20 times as potent as chlorothiazide.^{3, 2, 6, 7, 8, 12, 21} This in itself is of no great advantage since chlorothiazide is of an adequate potency. The fact that the patient is obliged to swallow a smaller tablet is not, in itself, a worthwhile outcome of the amount of research done on the subject. It has been claimed that hydrochlorothiazide and hydroflumethiazide have a more prolonged action than chlorothiazide,^{6, 28} and this might be an advantage. However, this effect seems to us to be variable. Individual differences between subjects make this sort of difference difficult to assess.

The greater potency of hydrochlorothiazide and hydroflumethiazide is almost certainly associated with the fact that a larger percentage of a given dose appears in the urine than with chlorothiazide.²⁸ This may be due to more efficient absorption from the intestine, or perhaps to the fact that while chlorothiazide is excreted in the bile, its derivatives are not, and thus more is available for renal excretion.⁷

Dose-response curves^{8, 13, 17} seem to show that while there is an increasing diuretic response with up to 50 or 100 mg. of the drug, no advantage is to be gained from administration of larger doses.

Renal Loss of Electrolytes

Sodium, Chloride and Bicarbonate

The efficiency of a diuretic is judged by its ability to increase the excretion of sodium and chloride by the kidneys, and using this criterion, there is no doubt that all the chlorothiazide group are very effective. In this respect there is little to

choose between chlorothiazide on the one hand, and hydrochlorothiazide and hydroflumethiazide on the other, if differences in potency are allowed for.^{28, 2, 6, 7, 13, 15} Water excretion is secondary to loss of these ions.

However, the 'ideal' diuretic results in an increased urinary loss of electrolytes in proportion to their concentrations in the extra-cellular fluid; that is, the ratio of Na : Cl : HCO₃ in the urine should be approximately 140 : 100 : 30. Any drug which alters these ratios will tend to cause a disturbance of acid-base balance. Thus acetazolamide, by increasing the excretion of bicarbonate in proportions greater than those given above, frequently causes a hyperchloraemic acidosis, while the use of mercurials, which results in very little bicarbonate excretion may lead to hypochloraemic alkalosis; both of these conditions are associated with the development of resistance to the drug. Chlorothiazide, by virtue of its mild carbonic anhydrase inhibitory effect causes more loss of bicarbonate than the mercurials, and although the ratio of sodium to chloride is about 1 to 1, trials have shown little or no tendency to acid-base disturbances. However, both its derivatives under consideration here have little effect on bicarbonate excretion, and both sodium and potassium are lost mainly in the form of chloride. It has repeatedly been observed that with these two drugs more chloride than sodium is excreted,^{3, 6, 13, 29} and as might be predicted there have been reports of the development of hypochloraemia.^{21, 25, 29} It may be that this will prove to be a drawback of long continued use of hydrochlorothiazide and hydroflumethiazide.

Potassium

As has been stated above, hypokalaemia is the greatest hazard of chlorothiazide therapy, and it was hoped that the risk might be less with its derivatives. However, this has not proved to be so,^{7, 11, 21, 29} and potassium supplements should be given with these drugs. The greatest loss of potassium occurs in patients with marked secondary hyperaldosteronism, particularly those with hepatic cirrhosis, in which the drug may precipitate hepatic coma, possibly as a secondary result of hypokalaemia.^{23, 15} Potassium loss is also aggra-

vated in subjects on strict sodium restriction, since less sodium is then available to balance the excretion of chloride and the deficit is largely made up of potassium.

For these reasons, patients treated with the chlorothiazide analogues should receive potassium supplements, probably on the days between the doses of the diuretic,²² and should be allowed salt in their diet. In addition, care should be taken with digitalis therapy, since sensitivity to this drug is increased by potassium depletion.²⁹

In passing it may be noted that some potassium loss occurs with mercurials, but that the much lower incidence of hypokalaemia in patients treated with them may be due to the fact that these drugs are usually given at longer intervals than chlorothiazide and its derivatives.

Other Effects

Effect on Serum Uric Acid

Hyperuricaemia has been reported during the use of hydrochlorothiazide as with chlorothiazide, usually in patients with renal disease.^{25, 29} However, clinical gout has rarely been observed and this finding is probably of little significance.

Effect on the Blood Pressure

Chlorothiazide has been reported to potentiate ganglion-blocking agents used in the treatment of hypertension by decreasing their excretion, and has also been reported to have a primary hypotensive effect, possibly due to a reduction in plasma volume.^{10, 5, 9} Similar effects have been described for hydrochlorothiazide and hydroflumethiazide.^{2, 29}

Effect in Diabetes Insipidus

Kennedy and Crawford¹⁴ have claimed that in diabetes insipidus chlorothiazide and hydrochlorothiazide have an *antidiuretic* effect, and suggest that these drugs could be used in treatment of the disease. Further reports are awaited, but in one case seen at Westminster Hospital this effect has not been confirmed.

Toxicity

The toxicity of the chlorothiazide group of drugs is very low. The greatest danger, as stressed above, is potassium depletion, especially in the case of hepatic cirrhosis. There have been reports of mild gastrointestinal symptoms such as abdominal distension and flatulence²¹ and transient skin irritation.⁶ These are rare and unimportant side

effects. The more serious complications of agranulocytosis and thrombocytopenic purpura have also been reported with chlorothiazide,^{30, 18} but these are very rare, and have not yet been reported with the analogues.

Summary

Hydrochlorothiazide and hydroflumethiazide are relatively safe oral diuretics.

Weight for weight, they are more potent than chlorothiazide.

Compared with the latter, the tendency to produce urinary potassium loss is not significantly reduced.

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