THE USE OF DIURETICS IN BRIGHT'S DISEASE

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Diuretics are substances which increase the volume of the urine by some modification of the complicated process by which urine is formed. Part of this process takes place outside the kidney, beginning with the absorption of fluid from the alimentary canal, and various metabolic processes take place in the tissues before urine is actually elaborated in the kidney. Diuretics, therefore, may be renal or extrarenal in their action. The mode of action and the site of action, in the case of most diuretics, is at best uncertain and may occur at various points in the tissues or tissue fluids, in the capillary walls or blood itself, in the general circulation or renal circulation, as well as in the renal tubules and glomeruli.

The generally accepted modern theory of renal secretion as formulated by Cushny offers a basis for a classification of diuretic agents which Solis-Cohen[1] suggested. According to this theory, there occurs a simple diffusion through the glomerular tufts of all the diffusible substances contained in the blood, the same proportion and concentration being retained. This filtrate then passes into the tubules where there is a resorption of most of the water and all or a great part of certain of the dissolved constituents of this glomerular filtrate. The residue of water, together with those dissolved substances which are not reabsorbed, constitute the urine. The reabsorbed substances are known as threshold substances, inasmuch as they appear in the excreted urine only when their concentration in the blood and hence in the glomerular filtrate exceeds an approximately fixed or threshold percentage. Substances such as sugar are normally not found in the urine during a state of health, since they rarely reach the level of overflow. An exception to this is seen in the so-called renal diabetes in which the renal threshold for sugar is apparently very low. Other substances, such as sodium chloride, are fairly constantly present in quantities above the threshold and consequently are excreted. The renal waste substances, chiefly urea, uric acid, creatinine, urates, phosphates, etc., which constitute the most characteristic constituents of urine, are not reabsorbed but appear in the urine in the same absolute quantity as in the filtrate and in much greater proportion.

The volume of urine secreted depends chiefly upon the following factors:

1. The quantity of renal circulation at any given time. This is dependent upon the general circulation as well as on the degree of contraction or dilatation of the renal vessels. It has been shown definitely that normally only a fraction of the glomeruli are active at any one

time. Theoretically, any substance which would increase the number of active glomerular units should increase urinary secretion.

2. The osmotic pressure exerted by the colloids of the blood. The greater the concentration of colloids in the blood, the more difficult it is for water and diffusible substances to escape through the glomeruli and, conversely, the more the dilution of the blood colloids, the more readily will a glomerular filtrate be formed.

3. The concentration of the filtrate itself. The more concentrated the filtrate, the less readily is water removed from it by reabsorption, due to the increased osmotic pressure within the tubule which tends to prevent passage of water back into the renal vessels.

4. The rapidity of flow in the tubules must introduce a mechanical element into the amount of urine secreted, since the greater the time allowed for reabsorption, the more complete this must necessarily be.

Diuretic agents may act in a number of different ways to modify the factors normally active in the production of urine. In general, they fall into distinct classes, as outlined by Solis-Cohen[1]:

1. Those agents which act upon the circulatory system, causing an increased flow of blood through the kidney, providing greater opportunity for glomerular filtration, and possibly resulting in increased activity of a greater proportion of the glomeruli at one time. The most important representatives of this group are digitalis, squill, strophanthin, and probably alcohol.

2. Agents acting directly on the kidney, increasing the permeability of the glomerular membrane for water or lessening reabsorption in the tubules. The chief representatives of this group are a number of purine derivatives, each of which contains the xanthine nucleus, notably caffeine, a trimethyl xanthine, and theobromine and theophylline, both dimethyl xanthines. The chief effect of caffeine is a stimulation of the entire nervous system and, in addition to its use as a diuretic, it is also used as a cardiorespiratory stimulant. The increased nervous irritability which results from its use is frequently a factor mitigating against its use as a diuretic and, for this reason, theobromine and theophylline have frequently been substituted. Theobromine is a dimethyl xanthine occurring naturally in cocoa. It is quite insoluble in water but its two soluble salts have been used. These are diuretin which is sodium theobromine salicylate and agurin or sodium theobromine acetate. Theophylline, or theocine in its synthetic form, is more prompt than caffeine or theobromine in its diuretic action, but its effect is less lasting. Like theobromine, it has little or no stimulating effect on the central nervous system. In contrast to caffeine, small doses are believed to cause coronary dilatation. The

oral dosages ordinarily employed are caffeine, two to five grains; caffeine citrate, two to eight grains; caffeine sodium benzoate, five grains; theobromine, five to eight grains; theobromine sodium salicylate or diuretin, ten to twenty grains; theobromine sodium acetate or agurin, eight to fifteen grains; theophylline or theocine, three to six grains; theophylline sodium acetate, two to eight grains.

3. Hydremic diuretics which act upon the blood, increasing the amount of water available for excretion. There are three subgroups:

a. Water alone acts by diluting the blood, lessening the amount of both crystalloids and colloids, and thus allowing a more ready diffusion through the glomerular capsule.

b. Those agents which increase the concentration of the blood crystalloids, raising the osmotic tension of the blood, and thus withdrawing water from the tissues. This group includes all the so-called saline diuretics, acetates, chlorides, citrates, lactates, nitrates, sulphates, etc., as well as urea and sugars.

c. Those agents which apparently act upon the plasma colloids, lessening their avidity for water. The mercurials, such as calomel, and the organic mercury compounds, novasurol and salyrgan, act in this way. A combination of a mercurial and purine diuretic has been prepared under the trade name of mercupurin and a chemically related drug, mercurin, has been prepared in the form of a suppository.

A rather miscellaneous group of diuretics is composed of the essential oils and uva ursi. The essential oils apparently owe their diuretic action to a renal irritation which possibly results in renal congestion and opening up of glomeruli. In larger doses, they cause strangury and renal retention. Thyroid extract also has some diuretic effect, as do small doses of pituitary extract. Larger doses of pituitary extract have a definite anuretic action.

The chief value of diuretics is in cases of disturbed water balance, that is, where there is retention of superfluous fluid in the tissues or serous cavities. Under such conditions, also, the clinical effect of the drug therapy is more readily demonstrable.

Hemorrhagic Bright's Disease

In hemorrhagic Bright's disease, we are dealing with an inflammation of the renal tissue in either an acute, subacute, or chronic form. Since we have no drug therapy which influences favorably the inflammatory process, it must be a principle of treatment that no harm or further renal irritation be caused by the medication. In the acute or initial phase of hemorrhagic Bright's disease, it would seem dis-

tinctly logical that no effort be made to stimulate renal function, inasmuch as it is apparent that the renal tissue is making use of its maximum capacity. The purine derivatives have been much used under such circumstances but it has not been demonstrated that the water output or urea excretion is notably influenced by this form of therapy. Urinary excretion may improve considerably after a few days of treatment, but this is probably explained on a basis of coincidental renal improvement. Circulatory stimulants, especially digitalis, may be tried for general supportive purposes but it is unlikely that they will result in any increased circulation in the already congested and swollen renal tissue. The use of large amounts of water is generally contraindicated in view of the edema which is apt to be present, although Volhard[2] has been successful at times in giving large amounts of water up to 1500 cc. at one time, in an effort to break down the so-called renal block. Similarly, the saline diuretics, which cannot be excreted readily owing to the pathological condition in the kidney, will simply increase the osmotic pressure of the blood and further reduce the tendency to urinary secretion. The use of urea in large amounts is also contraindicated because of the increased blood urea which is a feature of severe cases of this type. The administration of sugar solutions intravenously, on the other hand, may be extremely useful from the general supportive viewpoint when the gastro-intestinal system is severely disturbed and, because of this fact, some degree of secondary improvement in renal function may occur. The use of mercurials is definitely contraindicated, not only because of the nephrotoxic action of the mercury but chiefly because of the danger of retention of the mercury.

In the latent stage of hemorrhagic Bright's disease, the use of diuretic drugs is usually unnecessary and illogical. In this phase, the renal tissue has regained sufficient function to render the patient asymptomatic. Edema has disappeared and the nitrogenous waste products are at a normal level. Further stimulation of the renal tissue will result in very little effect and may increase the hematuria and albuminuria.

In the active chronic stage, the use of diuretics has a very limited sphere of usefulness. Digitalis should be given if there is any evidence of myocardial insufficiency and it has been shown that the action of this drug is not affected by the presence of renal insufficiency. Where there is marked reduction of renal function, it is not to be expected that an increased renal circulation of any degree can be produced by its use. The purine derivatives are also likely to be disappointing in their effect and, in case of marked renal impairment, their retention with toxic effects may be noted. The mercurials may be used with caution in the chronic active stage. They are of some value in reducing edema but care should be exercised to see that the albuminuria and hematuria are not increased by their use and to be sure that there is no danger of

mercurialism from their retention because of reduced renal function. The saline diuretics, especially potassium nitrate, may be tried.

Degenerative Bright's Disease

The term, degenerative Bright's disease, comprises a heterogeneous group of renal conditions which are characterized by the presence of large amounts of albumin and casts of all types in the urine, but the red blood cells characteristic of the inflammatory group are not found. Clinically, this condition is characterized by the most massive edema seen in renal conditions, and by the absence of the hypertension and acute episodes frequently encountered in the hemorrhagic group. Examination of the blood shows a deficiency of plasma protein, a factor which undoubtedly accounts for the development of the edema since the osmotic pressure due to the colloids is therefore correspondingly reduced. There is also a marked cholesteremia. Pathologically, the disease is characterized by a lesion of the tubular epithelium, the glomeruli remaining relatively normal. This is a type of renal lesion secondary to poisoning with the heavy metals as well as to the toxemia associated with pregnancy and infection. A well recognized subgroup is the cryptic or lipoid nephrosis of unknown etiology, regarded by Epstein[3] as being a general metabolic disturbance of protein metabolism, the renal lesion being secondary. Inasmuch as this group shows the highest degree of edema with a kidney which is apparently not the seat of inflammatory change, diuretics assume a much greater degree of importance in regard to treatment.

Improvement in the general circulation by the use of the circulatory group of diuretics is sometimes of value in this group and this is particularly true where there is an element of cardiac failure; in fact, with primary myocardial insufficiency, the secondary renal lesion which occurs with the development of albumin in the urine is undoubtedly a mild degenerative lesion of this type and very frequently the albumin disappears from the urine following improvement in the cardiac condition. The purine group of diuretics have relatively little value under such circumstances, causing only very slight reduction of the edema. In the presence of massive edema, the use of large quantities of water is, of course, contraindicated, and, similarly, the use of sodium salts is inadvisable on account of the hydropigenic quality of sodium. Potassium salts, especially the nitrate, are useful. The administration of urea in dosage of ten to twenty grams, three times daily, is frequently a very useful measure and will give satisfactory clinical results. Inasmuch as there is no tendency for urea retention in this type of renal lesion, its use is perfectly allowable. The intravenous use of hypertonic solutions of sugar may also be of distinct value and, in addition to the

diuretic effects which may be obtained, they are frequently of value as a source of available energy to those patients with disturbed function of the gastro-intestinal tract.

The use of the newer mercurials in this condition has been extremely successful. Calomel should not be used but novasurol and salyrgan, preferably the latter, have been extremely valuable. It is true that these preparations contain mercury and that mercury selectively poisons the tubular epithelium; however, if they are used cautiously, there seems to be no danger in their administration. They should not be used if there is a marked reduction of renal function or in the presence of severe anemia, cachexia, fever, or diarrhea. They may be given either intravenously or intramuscularly, although the intramuscular injection of novasurol is often fairly painful. It is well to begin with a test dose of one-half cc. which, if it produces no ill effects, may be increased within the next day or two to one to two cc., following which it may be given at intervals of two or three days until four or five doses have been given. Its action is undoubtedly considerably aided by the administration by mouth of sixty to ninety grains daily of ammonium chloride or nitrate, preferably the latter, for a day or two previously and continuously throughout the course of treatment.

In degenerative lesions of the kidney, the use of thyroid extract frequently produces striking diuretic results. Such patients usually have a lowered basal metabolic rate but, even with slight reduction of the metabolic rate, such patients will tolerate large doses of thyroid extract without experiencing any toxic effects. It has been demonstrated that toxic effects are not seen in the presence of the hypercholesteremia of this lesion and that the level of cholesterin in the blood may be used as a guide to thyroid therapy. Dosage should be started with one-half to one grain daily and gradually increased up to two or three grains daily if well tolerated and its use may be continued over long periods of time. Its mode of action is uncertain. It has been suggested that the resorption of salt solution from the subcutaneous tissues is slower in the animal with hyperthyroidism and that this is accelerated by the administration of thyroid extract. Epstein[3] believes that the beneficial effect is due to a stimulation of protein metabolism, an abnormality of which he regards as the fundamental basis of the disease and he uses the glandular products as an adjuvant to his high protein intake. In a few cases, particularly those associated with a disturbance of calcium metabolism and clinical manifestations of tetany, the use of parathyroid extract has given a good diuretic response.

Renal Lesions of Vascular Origin

In the renal lesion of vascular origin, edema is far more frequently of cardiac than of renal origin and, consequently, the general circulatory

group of diuretics is of most value, chiefly because of their cardiac action. In the earliest stages of essential hypertension, evidences of renal disease are entirely lacking but, as the condition progresses, small amounts of albumin, a few casts, and periodically some red blood cells may be found in the urine. At no time do the renal signs approach those seen in the hemorrhagic or degenerative group, and in only a small proportion of these cases does death result from renal insufficiency. The rationale for the widespread use of diuretics in this group of cases has apparently been based largely upon the conception that the etiology depended upon renal causes but there is no good evidence that the hypertension can in any way be affected by the use of any diuretic drug.

Digitalis is, of course, indicated in myocardial insufficiency and has been recommended by many to be of value in supporting the heart which has not shown signs of weakening. In the presence of failure and edema, it is of great value and, of course, secondarily improves the renal circulation. The purine derivatives have been widely used in this condition but their value would seem to be confined largely to extrarenal effects such as coronary dilatation. In this respect, theophylline would appear to be the most valuable drug. Saline diuretics similarly are of little value. The intravenous administration of sugar solutions, because of their nutritive and perhaps to a less extent of their diuretic effect, are very useful but it is important to remember that the circulation must not be loaded with too much fluid. Edema occurs rather rarely in the absence of congestive failure but, if present, the use of salyrgan, either alone or combined with ammonium nitrate, is of distinct value.

In general, it would appear that the use of substances designed to stimulate intrarenal activity has decreased markedly and that the emphasis in the study of diuretics now lies upon substances designed to assist the extrarenal processes incidental to the formation of urine.

References

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