Use of Modern Diuretics

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The USE OF DIURETICS was revolutionized some 6 or 7 years ago by the introduction of chlorothiazide, the first satisfactorily effective orally administered diuretic. The fact that at least two far more potent diuretics, also effective on oral administration, are probably close to release for general use makes it appropriate to take stock of the present situation and to consider the prospective benefits and dangers which may be anticipated from the widespread and possibly indiscriminate application of such powerful diuretic agents.

By its general definition, diuresis is any increase in urine flow. With respect to the purposes for which diuretics are useful, this definition is far too broad and can lead to misguided application. We will consider a diuretic agent to be one which can produce a negative balance of sodium by increasing the excretion of salt by the kidney. The ability to produce a negative balance is important since, for example, the administration of salt itself will generally increase sodium excretion by the kidney; this hardly conforms, however, to the purposes for which diuretics are generally used.

Purpose of Diuretics

The purpose in administering diuretics is generally to reduce the volume of extracellular fluid to or toward normal—that is, to eliminate and prevent the formation of edema. These ends are accomplished by causing the excretion of an amount of salt respectively greater than or equal to the intake. Of course, the excretion of an amount equal to the intake is an object to be sought through the use of diuretics only when the intake is greater than the patient can spontaneously excrete and when the intake cannot readily be reduced to a level which can be excreted by the patient without the intervention of diuretics.

One is not, however, concerned with maintaining a high salt output for its own sake, nor, with the exception of those situations in which mannitol has been used as an osmotic diuretic, in maintaining a high urine flow. This may seem self-evident, but failure to keep the true purposes in mind leads to statements like the following which recently appeared in a brochure dealing with a new diuretic: "Supplements of sodium chloride will not only obviate hypokalemia, but will also enhance the diuresis." Of course, in the situation referred to, the obvious way to obviate the hypokalemia is to give neither diuretic nor sodium chloride and not to worry about unnecessary diuresis. Despite time-honored practices to the contrary, except for the avoidance of concretions in kidneys and urinary tracts, there are very few situations in which, beyond the avoidance of dehydration, the maintenance of a high intake and output of fluid and salt has any demonstrable beneficial effect.

Actions of Diuretics

Theoretically a diuretic might increase the excretion of salt either by increasing the amount of sodium filtered at the glomeruli or by reducing the reabsorption of salt and water by the renal tubules. In actual practice it turns out that all of the useful diuretics produce their effects by interfering with the reabsorption of sodium from the tubule lumen. The nature of the biochemical mechanisms which are inhibited by diuretics are for the most part quite unknown, and this is particularly true with regard to the more generally useful agents, the thiazides and the mercurials as well as the newer prospective diuretics, ethacrynic acid, and furosemide.

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Based on a lecture "Modern Diuretics: Use and Abuse" given at the meeting of the American Heart Association, Miami Beach, Florida, October 16, 1965.
Those whose mechanism of action is more apparent—the inhibitors of carbonic anhydrase and the aldosterone antagonists—are in themselves rather weakly diuretic and useful only for limited purposes. Most of the powerful diuretics have been developed more or less empirically. The carbonic anhydrase inhibitors and the aldosterone antagonists were developed for those specific actions; unfortunately, the maximum to be attained by such effects turned out to be disappointingly small.

With regard to the transport mechanisms inhibited by each of the several series of diuretics, we are, perhaps, slightly better off although this question is by no means settled. The various segments of the renal tubule differ particularly in the proportion of salt to water which they reabsorb, and hence in their contributions to the formation of dilute or concentrated urine. Consequently by an examination of the effect of a diuretic on the ability to form a dilute or a concentrated urine, it is possible to infer something about the tubule segment in which sodium transport is inhibited. On this basis it is clear that most of the commonly used diuretics and the new ones, ethacrynic acid and furosemide, inhibit sodium transport in the distal tubule and, in some cases, in the ascending limb of the loop of Henle. The disputed point is whether or not any of these have significant inhibitory effects in the proximal tubule where the largest fraction of the filtered sodium is reabsorbed. In recent micropuncture studies on dogs we have not found any evidence that reabsorption in the proximal tubule is inhibited by hydrochlorothiazide, mercurial diuretics, ethacrynic acid, or furosemide. However, differences of opinion about inhibitory actions in the proximal tubule remain not only because of inferences from less direct studies, but because the results of some of the micropuncture studies on rats are not entirely in agreement with ours in the dog.

Although a knowledge of the site and mechanism of action of a diuretic may help in an understanding of what happens when a diuretic is administered and may serve as a guide in the development of new agents, it is not essential to the rational use of this type of drug. Given diuresis of a certain magnitude, the composition of the fluid varies within a relatively limited range, a range which narrows as the diuresis increases. A general knowledge of the relationship between urine flow and urine composition combined with an appreciation of the potency of various diuretics will generally provide an adequate basis for their use.

Variation in Diuretic Effects

The diuretics currently available differ widely with respect to the maximum diuresis that they can produce. The peak diuresis from mercurial diuretics in an individual pretreated with acidifying salts may amount to some 15 to 20% of the glomerular filtrate. The maximum effect from drugs of the thiazide group is not often more than half that amount and with the aldosterone antagonists, carbonic anhydrase inhibitors, and other lesser diuretics, the maximum effect is again much smaller. With ethacrynic acid and with furosemide the peak effects have been found to be as great as 30% or more of the glomerular filtrate. These figures, of course, represent what under most favorable circumstances may be observed at the transient peak. This peak is transient not only because the maximum drug effect may be of limited duration, but because diuresis of the larger magnitude alluded to can obviously not persist for very long before the individual runs out of fluid.

In an average size individual with a normal rate of glomerular filtration, 20% of the glomerular filtrate is about 35 liters in 24 hours. In fact, in clinical use, the effect to be expected with any of these agents is considerably smaller than the maximum. For the effect of a diuretic over a 24-hour period to average as much as half of the maximum is unusual, indeed. Nevertheless, the diuresis to be expected is related in a general way to these potencies, and this must be kept in mind, as these new and powerful diuretics become available, as an indication of the massive diuresis which may sometimes be
induced by their vigorous application. Because diuresis is inherently self-limited, however, it is perhaps more important that the extent of dehydration—that is, loss of extracellular fluid volume—at which diuresis ceases will, in general, be proportional to the potency of the diuretic and, with the most potent, a patient may be carried well below his normal dry weight before a new balance is struck.

**Potassium Depletion**

So far as we know all of the useful diuretics produce their effects by interfering with the reabsorption of sodium from the tubule lumen. It is, therefore, somewhat paradoxical that it is commonly observed that when a diuretic is administered the excretion of chloride exceeds the excretion of sodium. This is generally considered to be the consequence of delivery of increased amounts of sodium chloride to the site within the tubule at which potassium is exchanged for sodium and to a relative increase in the exchange of sodium for hydrogen ion. In any case, the excretion of chloride commonly exceeds that of sodium, the deficit of the latter being made up by potassium and ammonium ions. Since the capacity of the kidney for the excretion of ammonium and potassium ions is relatively limited and that for sodium almost unlimited, sodium will constitute an increasing fraction of the cation excreted as the magnitude of the diuresis increases. This does not mean that the loss of potassium may not be of major importance (although with an excellent response it is less likely to be so), but we can be certain that as the fluid loss exceeds 2 or 3 liters a day, the cation lost will be largely sodium. Thus, if we deal with a highly active diuretic, it adds little to say that the ratio of sodium to potassium in the output is high—this merely says in another way that the diuretic is highly effective. It reveals nothing about the propensity of the drug for producing loss of potassium.

The problem of potassium loss has become a subject of considerable interest and importance since the introduction of the thiazide diuretics. While all of the factors involved have not been fully elucidated, the source of the difficulty can be understood from a consideration of the mechanism for potassium excretion and the factors which affect it. The potassium which appears in the urine is derived almost completely, if not entirely, from the activity of the mechanism in the distal portions of the tubule system which, in effect, exchanges potassium ions, secreted into the lumen, for sodium ions which are simultaneously reabsorbed. The amount of potassium exchanged for sodium depends on a number of interacting factors, the most important of which, for our present purposes, are the activity of the exchange mechanism, which is stimulated by the salt-active adrenal steroids, and the amount of sodium that is available for exchange. (It should be noted that, on the basis of recent micropuncture studies in the rat, this statement is somewhat inaccurate in its details, but still an adequate description of the over-all nature of the process.) In essence, no matter how high the exchange capacity may be, relatively little potassium will be excreted if relatively little sodium is delivered for exchange. Thus, animals given very large doses of mineralocorticoids do not become depleted of potassium if they are kept on a very low salt intake, because the sodium load to the mechanism is not adequate to allow for potassium loss. Individuals who are accumulating edema are often much in the same situation. They have a marked reduction of sodium excretion—which, of course, is why they are accumulating edema—and this retention of sodium frequently is accompanied by hypersecretion of aldosterone. They are likely, therefore, to have an increased capacity to exchange sodium for potassium, but, because of virtually complete reabsorption of sodium before the end of the tubule is reached, they do not use this capacity. When, however, a diuretic is administered, reabsorption of sodium is depressed, more sodium is delivered for exchange, and potassium excretion is markedly increased. Even if the diuretic has an inhibitory effect on the exchange mechanism, as is the case with mercurial diuretics, the
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excretion of potassium may increase because even the reduced exchange capacity is greater than the sodium load had been before the diuretic was administered. Of course, if the diuretic does not inhibit the exchange mechanism, as is the case with most other diuretics, the increase in potassium excretion will be even greater.

Some edematous patients, particularly with cardiac failure, do not have very high rates of aldosterone secretion. Although some increase in potassium excretion accompanies diuretic administration in such individuals, initial potassium losses are likely to be rather modest. After they have responded to diuretics and restricted salt intake, however, the secretion of aldosterone increases and with it potassium loss is enhanced.

When we ask why the problem of potassium depletion became common only with the introduction of the thiazides, we are faced with several possible contributing factors. Before the advent of chlorothiazide, the commonly used diuretics were the organic mercurials and, as already mentioned, the mercurials have a specific inhibitory effect on potassium secretion. In my opinion, however, the switch to diuretics lacking this property is a relatively minor factor. It is the usual thing to observe a marked increase in potassium excretion when mercurials are administered to edematous individuals. Such losses, if continued, are quite adequate to produce significant potassium depletion.

Another factor to be considered and dismissed is carbonic anhydrase inhibition. Marked increases in potassium excretion are produced by inhibition of carbonic anhydrase and chlorothiazide has significant activity as an inhibitor of this enzyme. However, the numerous derivatives of chlorothiazide which have since been introduced have greatly reduced potency as carbonic anhydrase inhibitors relative to their potency as inhibitors of sodium reabsorption; nevertheless, their use has not significantly diminished the problem of potassium depletion.

The important change which came with the introduction of the thiazides was, I believe, the change in the type of schedule by which diuretics are administered. The mercurials were usually administered at intervals of several days to a week, although occasionally under special conditions, particularly in hospitalized patients, they were administered more frequently. The usual pattern, however, allowed a considerable interval between doses during which interval the patient was quite free of the diuretic effect. If on the day of diuresis he incurred a deficit of potassium, he had several days to recover his losses from his normal dietary intake.

With the introduction of the thiazide group of diuretics, this pattern was changed. It was just as easy, if not easier, to administer the diuretic daily and to extend the period of the diuretic effect by giving it in divided doses. Thus the patient is more or less continuously under the effect of the diuretic, and even if the losses of potassium have no high peaks, there is no opportunity for the excretion to drop to a low level and for the patient to begin to make up his losses from his diet. Of course, if potassium intake is increased sufficiently by supplements, an adequate balance can be maintained, but it would, I believe, be more effective and easier to omit the administration of the diuretics for a few days at a time. As far as I know, however, this has never been tried systematically.

The point is particularly worthy of note when we consider the new diuretics just over the horizon. Their capacity to produce sodium depletion and hence to stimulate aldosterone secretion is almost certainly far greater than that of the thiazides, and their continuous administration to maintain "dry weight" in patients who have lost their edema will almost certainly lead to potassium problems among others.

Relation of Water and Salt Losses

Turning now to another aspect of diuretic effects, we should consider the proportions of water to salt in the losses incurred. The practice of restricting salt intake for the treatment of edema is based on the fact that the

Circulation, Volume XXXIII, May 1966
regulation of the salt content of the body and the total concentration or effective osmotic pressure of the body fluids are regulated by separate, although interdependent mechanisms. The activity of the osmoreceptor-antidiuretic hormone–renal tubule system normally maintains the osmotic pressure of body fluids within relatively narrow limits. If solute is lost from the body fluids, the resulting lowering of osmotic pressure normally leads to the loss in the urine of an equivalent volume of water and the restitution of osmotic concentration to normal. The regulation of salt content in turn relates, through poorly understood mechanisms, to the change in volume which has been incurred. As long as the system regulating osmotic pressure is operating normally, salt loss through restricted intake or through loss in the urine will lead to equivalent losses of extracellular fluid volume. However, we must remember and be on the lookout for the not uncommon instances in edematous patients in which the regulation of osmotic pressure is no longer effective and hyponatremia develops.

Contrary to the commonly held belief, hyponatremia does not result, certainly not directly, from massive losses of salt in the urine. It is characteristic of the renal processes for forming dilute and concentrated urine that the absolute amount of water which can be withheld to render the urine concentrated or the absolute excess of water which can be excreted in making the urine dilute is limited. When the excretion of solute is very low, the urine can be concentrated quite effectively, but as the amount of solute excreted increases, the concentration of the urine falls rapidly, and approaches isotonicity with extracellular fluid. Thus no matter what diuretic we use, if a massive diuresis ensues, we can be quite certain that the urine excreted will be close to isotonic with body fluids. This is all the more the case with mercurial diuretics which impair the process which leads to removal of water to render the urine hypertonic and with the new diuretics, ethacrynic acid and fursemide, which knock out this mechanism virtually completely. Of course, the loss of an isotonic sodium chloride solution cannot depress the sodium concentration of extracellular fluid. As the loss of salt induced by the diuretic decreases, the urine may become more concentrated but at the same time the reduced salt loss is not adequate to yield a significant lowering of the osmotic pressure of body fluids—that is, of the plasma sodium concentration.

**Hyponatremia**

This being the case, why does hyponatremia occur in patients treated with diuretics, as it most certainly does? Two groups of patients are involved and they represent the two ends of the spectrum of responsiveness to diuretics. At one end we have the group of highly resistant patients, with advanced cardiac failure or cirrhosis who are markedly edematous and who respond poorly to most measures including diuretics. These patients are clearly not hyponatremie because they have lost salt in response to diuretics as they usually lose practically none. They are hyponatremic because their disorder of electrolyte excretion has extended to involve a disorder of water excretion. This disorder is the result of one or both of two factors: (1) the fraction of the glomerular filtrate which reaches the segment of the tubule in which the urine is diluted is too small to permit the excretion of dilute urine and (2) there is secretion of antidiuretic hormone for reasons unrelated to the normal stimulus—an increase in the effective osmotic pressure of the body fluids. Such patients present a difficult problem in therapy. Nothing is gained by attempting to correct their hyponatremia by the administration of salt. This only increases their edema. If any measures to improve their circulatory status remain to be carried out, such therapy offers the best prospect of successful management of their hyponatremia. Otherwise the only effective measure is a rigid restriction of fluid intake which, unfortunately, is often resisted by the patient and only very slowly effective at best since it ordinarily involves a negative water balance of only a few
hundred milliliters a day in the face of an excess of water which may be of the order of 5 to 10 liters. In the treatment of severe cardiac failure, restriction of water intake should be more generally practiced to arrest dilation before it has become severe.

The other group of patients in whom hyponatremia develops are those who have responded well to diuretics and who have not only lost all of their edema but have gone past this point to a depletion of their extracellular fluid volume. They have developed a borderline circulatory insufficiency and, as in those patients with circulatory insufficiency of cardiac origin, fail to excrete water normally and, presumably for the same immediate reasons, namely, secretion of antidiuretic hormone for reasons unrelated to osmotic pressure and inadequate delivery of fluid to the diluting segment of the nephron. The indicated treatment is different from that in the other group of patients. In this case, the administration of sufficient salt to restore a normal volume of extracellular fluid will permit the normal regulation of water excretion.

Potential and Limitation of Diuretic Therapy

From these general considerations concerning diuretics and their effects, we may turn to a review of the potentialities and limitations of current diuretic therapy. The general conclusion one must reach from such a review is that, on the whole, the current situation is a rather favorable one.

The thiazides constitute the group of diuretics which are the most generally used. In considering these as a group rather than as a dozen or more individual drugs, I am proceeding from my conviction that there is little if any basis for distinguishing any one from the others. Possibly chlorothiazide itself stands a little below the rest because of its relatively higher activity as a carbonic anhydrase inhibitor, which property could conceivably contribute an undesirable increase in its tendency to produce potassium loss. Even in this case, however, the extent of carbonic anhydrase inhibition is unlikely to be sufficient to be a factor as the drug is generally used. With the others this problem disappears virtually completely. Various claims have been made that one or another of the drugs of this group produces less potassium loss than the others. There is good ground for extreme skepticism concerning this point. As indicated earlier, the induction of potassium loss is a nonspecific property of diuretics and of the circumstances under which they are used. I do not believe that an adequate controlled study would bear out any of these claims.

The thiazides also differ among themselves in the exact magnitude of the dose required to produce a particular effect. This, too, is a trivial matter. The ratio of toxic dose to effective dose is extremely high for all of these drugs so that a somewhat lesser potency on a weight basis is easily compensated for by an increase in dosage. The only consideration of importance is the effect observed when the dose is adequate to produce a maximum effect. In this respect the members of the group are identical.

Side effects other than those directly attributable to the diuretic action of this group have, on the whole, been minor. Some interference with urate excretion has been generally encountered, and the fact that similar effects have already been noted with ethacrynic acid and with furosemide suggests that this may be a general property of effective diuretics. This is not often of clinical consequence but should be watched for. The addition to the regimen of a uricosuric agent might be desirable in occasional instances. Disturbances of carbohydrate metabolism have also been found in patients receiving thiazides. No serious or irreversible consequences have been established, but the problem should be kept in mind.

Potassium depletion which we have already discussed is not an effect unique to this group of diuretics. My own preference for its management is to try intermittent therapy when other considerations do not require more intensive administration. Potassium supplements can be used if necessary, but they should be adequate. An additional 8 or 10 mEq per
day in an individual whose dietary intake is likely to be 60 or 70 mEq is not likely to make much difference. High potassium foods are greatly to be preferred since gastric irritation from pure potassium salts is a common problem and since the danger of intestinal ulceration and stricture from the administration of enteric-coated potassium salts has become apparent. The use of potassium-diuretic combinations is, in my view, to be discouraged since the amounts of potassium in these are, on the whole, rather small and are unlikely to balance the requirements of any particular individual patient, but, nevertheless, give a false sense of security.

The aldosterone antagonists and triamterene, which, although not an aldosterone antagonist, have very similar effects, are, by themselves, rather weakly diuretic. While they may be valuable in an occasional relatively easily maintained patient, there may be reason to question whether such patients really need diuretic therapy at all. The chief value of these agents is, in combination with other more effective diuretics, in reducing losses of potassium and correspondingly increasing sodium loss, particularly in the more diuretic-resistant patient. Some caution and frequent checks are, however, advisable since it is not difficult, at times, to induce an undesirable degree of potassium retention and hyperkalemia.

The mercurial diuretics remain, of those diuretics generally available, the most potent and effective. In the sick and diuretic-resistant patient they are still most likely to be effective, particularly if the ground is prepared by the administration of acidifying salts. The replacement of this use of the mercurials is probably the most immediate place for ethacrynic acid and fursemide which are likely to become available in the near future. They have the advantages of being not only at least as potent as mercurials in causing massive diuresis but are effective and relatively nontoxic on oral administration and their efficacy is not dependent upon the acid-base status of the patient. The difficulty in acidifying the patient in order to obtain the maximum effect from mercurials has often been a major problem, and it can be entirely circumvented with these new agents.

An additional place for fursemide may prove to be in the treatment of acute cardiac failure with pulmonary edema. The onset of massive diuresis within a few minutes of the drug's administration could be a valuable property in the management of this problem.

Caution with New Agents

It is appropriate to conclude with a note of caution concerning the widespread use of these new agents. The vast majority of patients in whose treatment the use of diuretics is indicated are well managed with the thiazide group of drugs and have little to gain from the availability of new and more powerful agents. Such agents should find their immediate place where currently available therapy is inadequate and should replace currently satisfactory treatment only when it has been shown that the hazards do not exceed the limited potentialities for improvement. The tendency to switch to the newest and most potent agent available could, in this area, lead to a situation in which striking benefits to a few patients are more than outweighed by the unnecessary problems incurred in the many others.

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On Dropsy (Circa 1680)

1. The finger, if pressed upon the lower part of the legs, will leave a mark, especially towards evening. In the morning the impression is less distinct. This is the first sign of the disease, especially if there be difficulty of breathing besides. Not unfrequently, however, pregnant women, and women with whom the menstruation has ceased, as well as men suddenly freed from inveterate asthma, have swellings of the same sort. When the feet and legs are stretched to their utmost, the waters rush into the abdomen, and this they gradually distend to its full capacity. At length, they reach the nobler viscer, and the patient dies.

In proportion as the parts occupied by the disease increase, the rest of the body loses flesh, whilst dyspnoea, scantiness of the urine, and intense thirst, supervene._The Works of Thomas Sydenham, M.D., vol. 2. London, The Sydenham Society, 1850, p. 275.
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Circulation. 1966;33:802-809
doi: 10.1161/01.CIR.33.5.802

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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