



The Pharmacology of Newer Diuretics

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Diuretics continue to be among the commonest of all prescribed items. Until recently, the physician needed to have little concern about the dose of the agent he was choosing because firstly, the dose-response curve tended to be startlingly flat, and secondly, there was little chance of inducing an excessive diuresis, regardless of dose. Now that furosemide (Lasix) and ethacrynic acid (Edecrin) have become available, we find that one must indeed titrate the dose to the particular patient, and must appreciate for the first time the complications which can result from an excessive diuresis. Finally, with the availability of triamterene and MK-870 (Colectril, not yet available), one must appreciate the importance of the distal tubular mechanism for potassium for sodium exchange. The additive effect of these exchange inhibitors can be of considerable clinical usefulness.

Adverse Effects of Diuretics

Figure 1 illustrates the excessive diuresis which can result from the newer, more potent diuretics. This patient was hospitalized and started on what seemed like a reasonable dose of ethacrynic acid, but she lost 35 pounds in four days. Fortunately, this patient had no adverse effects, but this is the very circumstance in which the series of adverse effects shown in table 1 can occur. The most important of these is hypovolemia. This is particularly likely to occur in the patient with cirrhosis or nephrosis.

The problem is one of developing circulatory collapse, shock. The only treatment advisable then is the infusion of salt-poor albumin. Such episodes have been reported with some real frequency. The problem of inducing excessive potassium loss is primarily related to the patient who is also taking digitalis and who becomes much more susceptible to the ectopic activity of the cardiac glycosides. Hypochloremia will induce diuretic refractoriness to mercurials, but not to these new agents. In spite of electrolyte derangements and in spite of reduction in renal blood flow, furosemide and ethacrynic acid will continue to exert diuretic effects. Hyponatremia may develop, particularly in the patient who is having a marked saluresis and who replaces the volume with tap water. The cause of muscle cramps, the weakness, the "washed-out" feeling, is still not clear, but the symptoms are well-recognized in patients in whom a marked prompt diuresis ensues. The relationship to thrombosis and the development of gout are not clear, but there is some circumstantial evidence suggesting that these can occur during diuresis. In summary, one must avoid having too rapid and too massive a diuresis.

Table 2 suggests some measures to avoid adverse effects of diuretics. The most important is the first: choose a sub-maximally effective dose. This requires knowing something about the dose response to these new agents. The only way to judge the response, of course, is to

TABLE 1

Results of Excessive Diuresis

1. Hypovolemia
 - a. Reduction in renal blood flow
 - b. Circulatory collapse
2. Hypokalemia
 - a. Digitalis intoxication
3. Hypochloremia
 - a. Mercurial refractoriness
4. Hyponatremia
 - a. Water intoxication
5. Muscle cramps
6. Weakness
7. ? Thromboses
8. Acute gout

TABLE 2

Routine Measures on Initiating a Diuresis

1. Choose a submaximal diuretic dose.
2. Record weights and fluid balance.
3. Restrict activity.
4. Reduce sodium intake.
5. Restrict fluids to 1 to 1.5 liters, especially the day after diuresis.
6. Watch blood Na, K, Cl, HCO₃, urea and hematocrit.

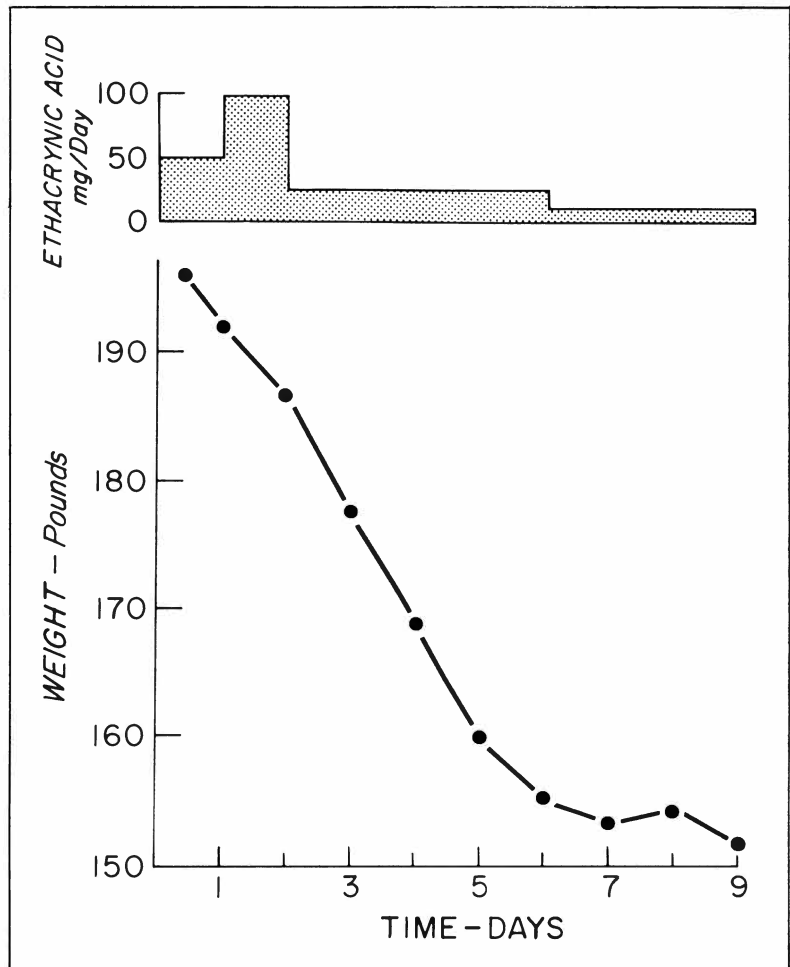


Fig. 1—An excessively rapid response to ethacrynic acid.

record weights and fluid balance. Weights must be recorded by every out-patient who is taking diuretics for their diuretic properties. If a poor response from the diuretic occurs, restricting the patient's physical activity during the day will often enhance the diuresis, since in heart failure, physical activity reduces renal blood flow. Fluids need be restricted only if the patient appears to be one who has the habit of ingesting water following a marked diuresis. No simple rule can be offered for the frequency of determining serum electrolytes. If the patient is having a marked response, they should be checked. Obviously, if he is hav-

ing a poor response, they should be checked. With the new agents which continue to be effective even in the face of electrolyte abnormalities, it is necessary to check them with some regularity, like once every week or two.

Quinethazone

The first new agent to consider is quinethazone (Hydromox). Figure 2 shows the structural formula for quinethazone. Note the similarity to chlorthalidone (Hydroton) and to chlorothiazide (Diuril). Quinethazone is thus another one of the large group of thiazide derivatives. It has no particular ad-

vantage with the exception of a more prolonged activity. In this sense it more closely resembles chlorthalidone. It has no other advantages and no other disadvantages.

Furosemide

The structural formula for furosemide (Lasix) is shown in figure 3. Furosemide has also been called furseamide and frusemide. This is an agent whose activity-structure relationship is still not clear. Some would suggest that it is the common grouping with the thiazides; others would suggest that it is the free carboxyl group which is re-

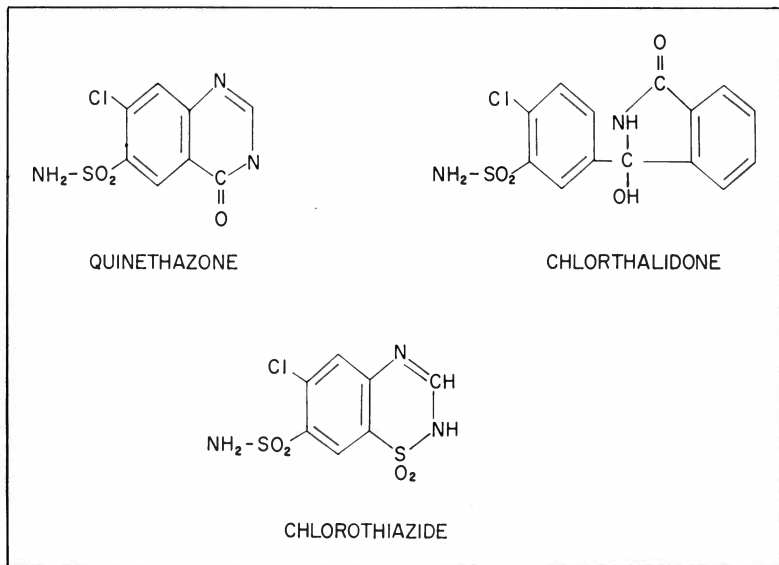


Fig. 2—Structural formulae of quinethazone (Hydromox), chlorthalidone (Hygroton), and chlorothiazide (Diuril).

responsible for its diuretic activity. It is clear that it is different from the thiazides in several ways. Firstly, it is active in an animal in which there is no liver. The thiazides require the presence of the liver before diuresis will ensue. Secondly, furosemide causes a decrease in bicarbonate excretion in contrast to the typical thiazides. Thirdly, there is a markedly different order of efficacy. Furosemide clearly works in the ascending loop of Henle. It probably works in the proximal tubule, although animal micropuncture studies give contrary evidence. It has been said, though, and we have all been taught, that some 80% of the normal glomerular filtration is reabsorbed in the proximal tubule. If a diuretic were 100% effective, theoretically it could only increase urine output to 20% of the filtration rate if it had no activity in the proximal tubule. Furosemide can produce a diuresis of as much as one-half of the glomerular filtration rate, and this has been used as evidence that it must alter the proximal tubular reabsorption of salt and water.

Figure 4 shows the human response to furosemide contrasted with hydrochlorothiazide at 50 to 75 mg of each. Note that furosemide produces a larger diuresis, natriuresis and chloruresis, but importantly, no greater kaliuresis. For each milliequivalent of sodium excreted, furosemide causes less potassium excretion than do the thiazides.

Furosemide is very rapidly effective, acting in minutes when given intravenously. Its maximum effect occurs within two hours when given orally. The dose response curve is shown in figure 5. In the case of hydrochlorothiazide, increasing the dose from 50 to 100 mg causes only a modestly increased natriuresis, whereas increasing the dose of furosemide from 50 to 100 mg causes a very considerable difference. Furose-

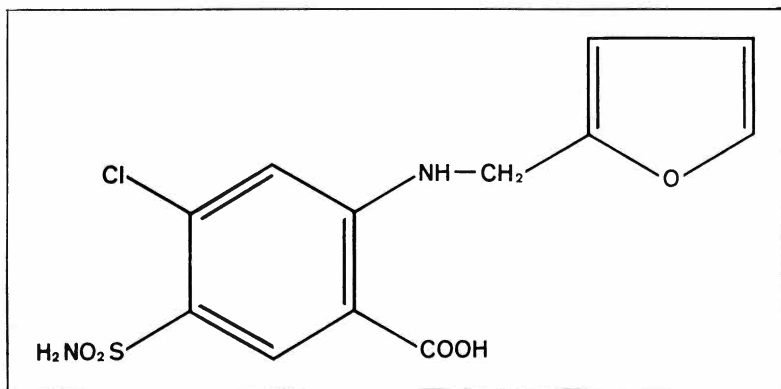


Fig. 3—Furosemide (Lasix), 4-chloro-N-(2-furylmethyl)-5-sulfamoyl-anthranilic acid.

mide, therefore, differs in potency, that is, more diuresis per milligram, but more importantly, it differs in efficacy, giving a maximum response beyond what can be achieved with any of the thiazides.

The toxicity of furosemide is still under investigation. Table 3 lists the toxic reactions. Rare hypersensitivities, usually rashes and rare, not definitely causally-related alteration in blood counts have been reported. Nausea and vomiting appear to be clearly dose-related and will occur quite frequently at single doses exceeding 200 mg. Furosemide causes hyperuricemia regularly and will precipitate acute gout occasionally. Pancreatitis and hyperglycemia have now been reported in association with furosemide therapy, but are not yet established clearly as causally related. The extent of the hyperglycemia appears to be considerably less than that which occurs with the benzothiadiazines. The major problem with furosemide is excessive diuretic effect. This is the major adverse effect in the use of this agent.

In summary, then, furosemide is some three to five times as efficacious as the thiazides and causes less potassium loss. Because it is so rapidly effective, it has been used in the treatment of pulmonary edema and in cerebral edema. It is important to note that it has a steep dose response curve and that it continues to be effective even in the face of electrolyte derangement, hypovolemia, and azotemia.

Ethacrynic Acid

The structural formula for ethacrynic acid (Edecrin) is shown in figure 6. Note here the absence of the sulfamyl group, but again the hallogenated cyclic structure. The free carboxyl group is thought to be a major determinant of its activity. This agent appears to work on the identical tubular mechanisms affected by furosemide. If one gives a maximally effective dose, of

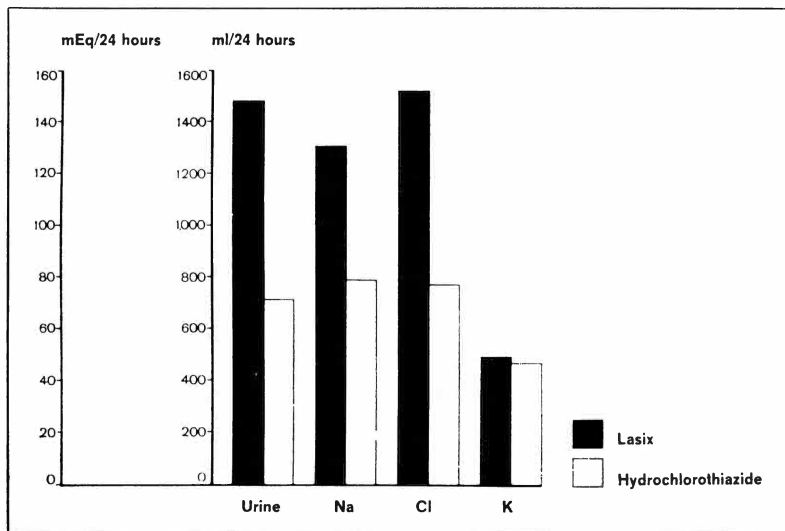


Fig. 4—Urinary response to equal milligram doses of furosemide and hydrochlorothiazide (Reproduced with permission from International Furosemide Symposium, fig. 27, 1963).

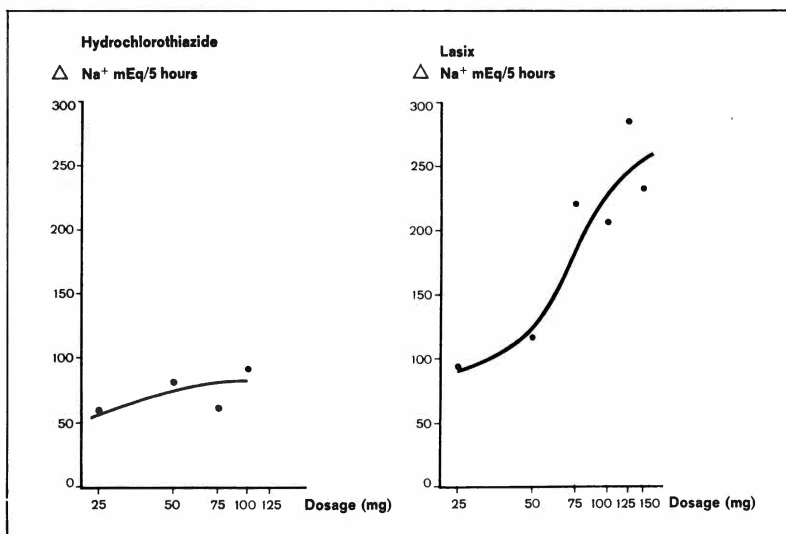


Fig. 5—Dose-response curves for hydrochlorothiazide and furosemide based on natriuretic effect (Reproduced with permission from International Furosemide Symposium, fig. 9, 1963).

either furosemide or ethacrynic acid, and then gives the other agent, no further response ensues. This would tend to indicate that the same mechanisms are affected by the two agents. Figure 7 shows the pattern of electrolyte excretion; a marked chloruresis, natriuresis, diuresis, and a minimal kaluresis. This is similar to the pattern shown for furosemide (fig. 4). When ethacrynic acid is given intravenously, an extremely prompt and massive response can be expected. Ethacrynic acid is available for parenteral use and is recommended in the treatment of pulmonary

edema. A diuresis of 500 or 600 ml in one hour is not unusual. This is equivalent to using a phlebotomy or venous tourniquets to reduce the circulating blood volume. Figure 8 illustrates the response of one such patient. One and one-half liters of urine had been passed in one hour after 50 mg of intravenous ethacrynic acid, and about 3 liters by three hours.

The dose response curve is also shown in figure 7. There is an increasing response until one reaches a dose of 200 mg, and at that point maximal therapeutic effect has been achieved. So again, there is

a very steep dose response relationship. One patient whom we treated in the metabolic ward is shown in figure 9. Note that with gradually increasing doses from 50 to 100 mg, there was essentially no response in weight. With an increase to 150 mg, there ensued a slow but steady diuresis until dry weight was obtained. This was a patient known, from our previous experience with her, to have highly resistant congestive heart failure.

Table 4 indicates the toxicity, which is probably identical to what was listed for furosemide. Rare rashes and thrombocytopenia have

TABLE 3

Toxic Effects of Furosemide

1. Rare hypersensitivity
2. Nausea, vomiting (dose related)
3. Hyperuricemia and gout
4. Pancreatitis
5. Hyperglycemia
6. Excessive effect
Hypovolemia; hypochloremic alkalosis; hypokalemia; hyponatremia

TABLE 4

Toxic Effects of Ethacrynic Acid

1. Rare hypersensitivity
2. Nausea, vomiting, diarrhea (dose related)
3. Hyperuricemia and gout
4. Tinnitus, vertigo, deafness
5. Excessive effect
Hypovolemia; hypochloremic alkalosis; hypokalemia; hyponatremia

TABLE 5

Toxic Effects of Triamterene

1. Rare hypersensitivity
2. Nausea, vomiting, diarrhea (dose related)
3. Azotemia
4. Hyperkalemia

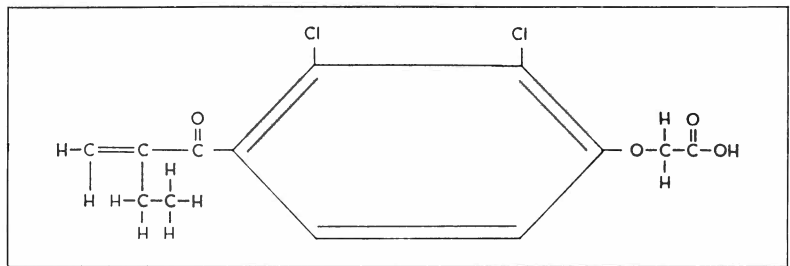


Fig. 6—Ethacrynic acid (Edecrin), 2, 3-dichloro-4-(2-methylenebutyryl) phenoxyacetic acid.

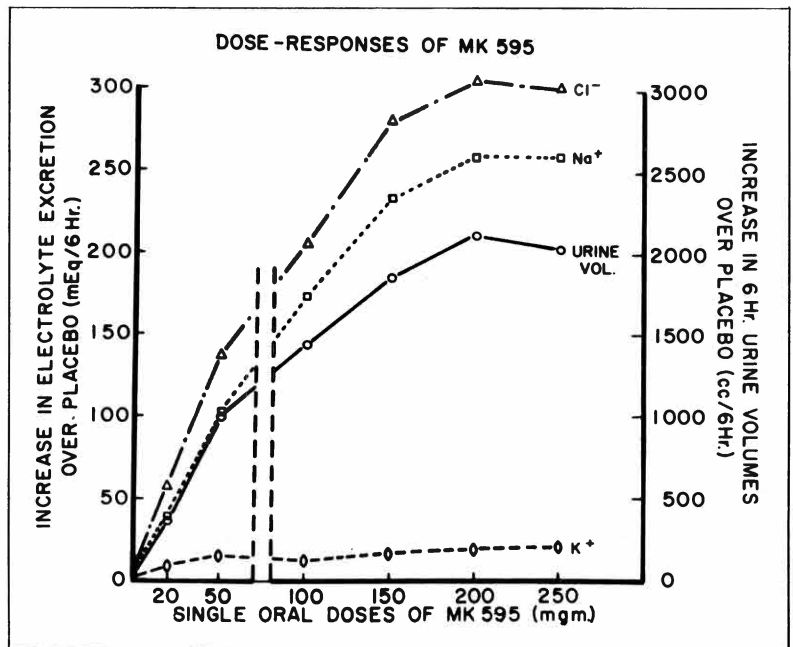


Fig. 7—Urinary response to graded doses of ethacrynic acid (Reproduced with permission of Merck, Sharp & Dohme Research Laboratories).

been reported; nausea, vomiting, and diarrhea appear to be dose-related. Hyperuricemia and gout will occur. Tinnitus, vertigo, and deafness have been reported with ethacrynic acid. It would appear to be a function of the acute change of the dynamics across the inner ear endolymph, since continued therapy with the agent is not associated with continuing or worsening of these symptoms, but rather they tend to disappear over a few days as soon as fluid balance appears to be more stable. This is probably not toxicity in the usual sense any more than excessive effect is toxicity, but is an extension of the pharmacologic properties of these rapidly and potently active diuretic agents. Excessive effect was considered earlier.

Ethacrynic acid, then, is also a potent, highly-effective diuretic. It continues to be active in the face of electrolyte derangements and azotemia. It is available for intravenous use and probably has a real place in the treatment of the patient with acute pulmonary edema in addition to our usual measures.

Triamterene and Amiloride

Turning now to agents that act by entirely different mechanisms, triamterene (Dyrenium), now available, and amipramizide or amiloride (Choletril) (MK-870), not yet available, are shown in figure 10. The similarity in the structures is evident. There is a considerable difference in the potency as triamterene is given in doses of 100 to 200 mg and amiloride is given in doses of 5 to 30 mg. These are the agents which act to block the sodium-potassium exchange mechanism in the distal tubule. This is totally different from any of the activities of the other two agents described above. They are similar in effect to spironolactone, but spironolactone is a competitive inhibitor of aldosterone and is thus only effective in the

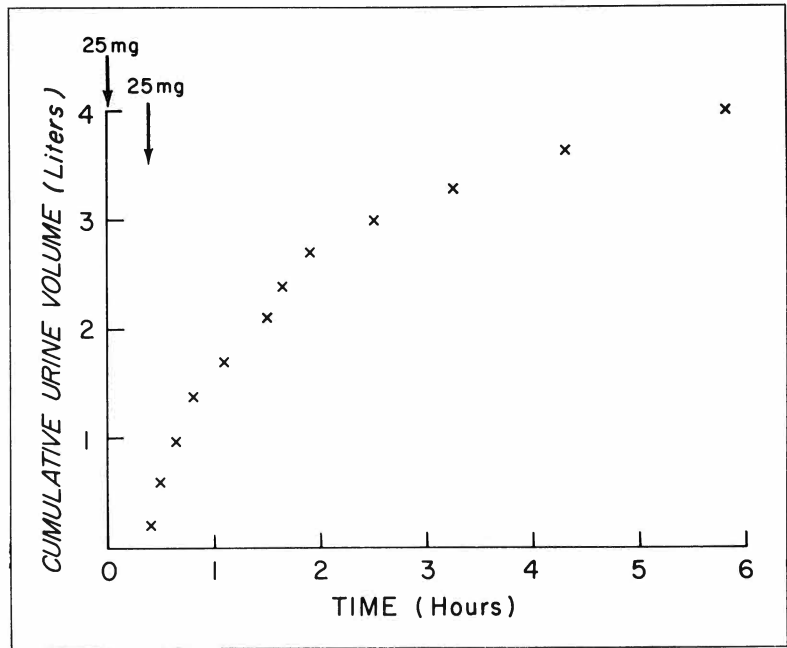


Fig. 8—Urine volume (cumulative) following intravenous administration of ethacrynic acid in a patient with acute pulmonary edema occurring in the course of chronic congestive heart failure.

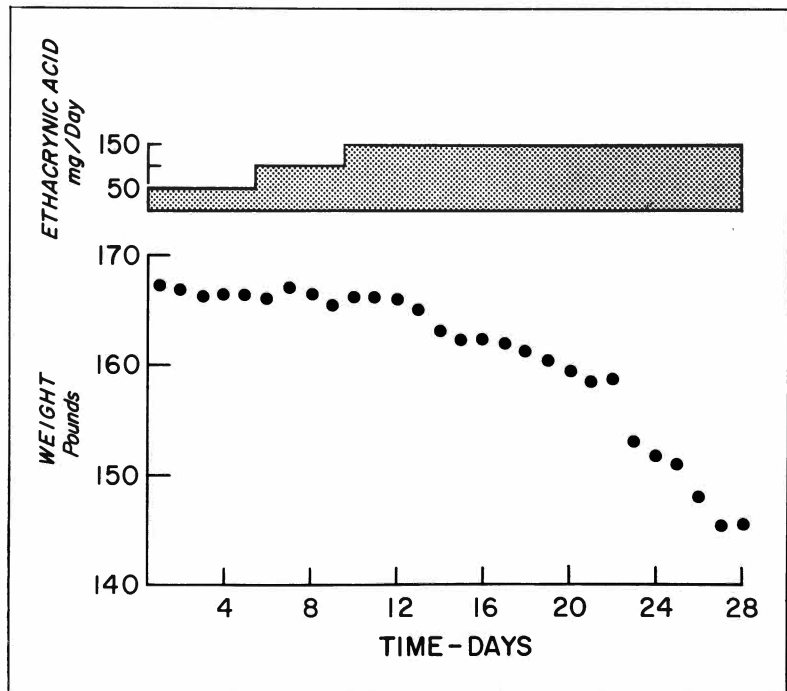


Fig. 9—Response to graded doses of ethacrynic acid in a patient with diuretic-resistant chronic congestive heart failure.

presence of aldosterone. These agents block this tubular reabsorptive mechanism regardless of whether aldosterone is present. In this way they tend to be more effective and do not require that the patient be in a state of induced hyperaldosteronism.

One can then predict the diuretic response. Figure 11 depicts a modest increase in sodium excretion and a decrease in potassium excretion in response to triamterene. Essentially a maximal effect results from a dose of about 100 mg of triamterene. These agents are modest in their natriuretic effect.

Something of the toxicity is noted in table 5. Again rare hypersensitivity and dose related nausea and vomiting are listed. Azotemia has been interesting in that slight, but significant increases in blood urea nitrogen have been recorded. They tend to stabilize and have not generally been a cause of significant concern. The problem with these agents is the development of hyperkalemia. When given either alone or in conjunction with thiazides, triamterene and amiloride may cause serious and even fatal hyperpotassemia. There is no way to predict in a given patient the exact response. Potassium levels must be checked in patients receiving such therapy.

In summary, these two agents, triamterene and amiloride have a modest natriuretic effect, about one-half to one-fourth that of the thiazides. They cause potassium retention, and most importantly, they are additive in effect to the other diuretics, thiazides, furosemide, and ethacrynic acid. Figure 12 illustrates this additive effect. This is the same resistant patient (fig. 9) treated on an out-patient basis receiving furosemide. Note that 40, 80, 160, and even 240 mg of furosemide per day was associated with no significant weight loss. At this point triamterene was added to this steady regimen, and the patient achieved a weight loss of approximately a pound per day over

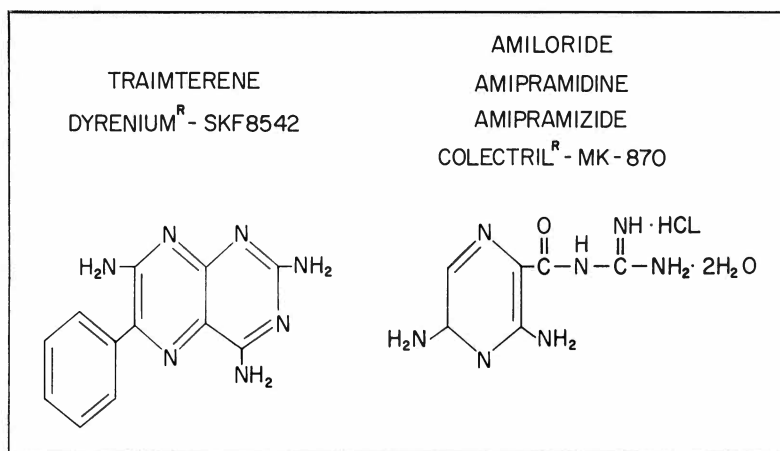


Fig. 10—Structural formulae of triamterene (Dyrenium) and amiloride (Colectril).

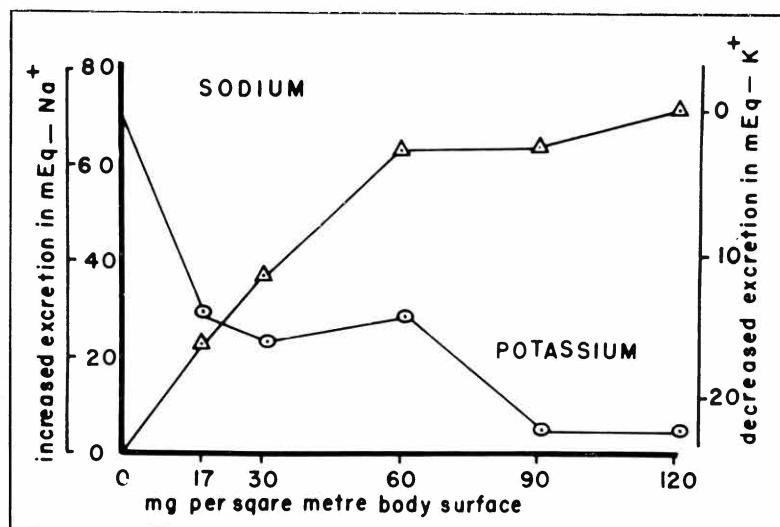


Fig. 11—Dose-response for triamterene (Dyrenium) depicting urinary sodium and potassium response.

the next two weeks. These agents have not been shown to induce hyperglycemia or hyperuricemia and may have some special advantage in patients in whom these are problems.

Some of the typical effects of differing types of diuretic agents can be noted in the results of a study we have done.* Twelve patients with chronic congestive heart failure, hospitalized on our metabolic ward on constant sodium and fluid intake, were each given ethacrynic acid, triamterene and hydrochlorothiazide. Each patient received all three drugs, one on each of three successive days. The order of administration was so randomized that each drug was given with equal frequency on the first, second, and third days. 100 mg of each diuretic was given at 8 AM and again at noon. Carry-over effect was minimized since 20 hours separated the successive drugs.

Statistical analysis indicated no significant variation due to the order of drug administration or to the pattern of individual patient response. There were, however, statistically significant differences in the responses to the three diuretics.

Ethacrynic acid effected a significantly greater weight loss, natriuresis, chloruresis, and diuresis than did hydrochlorothiazide or triamterene and did so in both the first four hours and for the 24 hour period (fig. 13). Hydrochlorothiazide resulted in a somewhat greater diuresis, natriuresis, and chloruresis than did triamterene, but these differences were not statistically significant at the 5% level of probability.

On the other hand, triamterene resulted in significantly less kaliuresis than either ethacrynic acid or hydrochlorothiazide. The potassium excretion with the latter two was not significantly different.

This study, then, substantiates the greater potency (diuresis, salu-

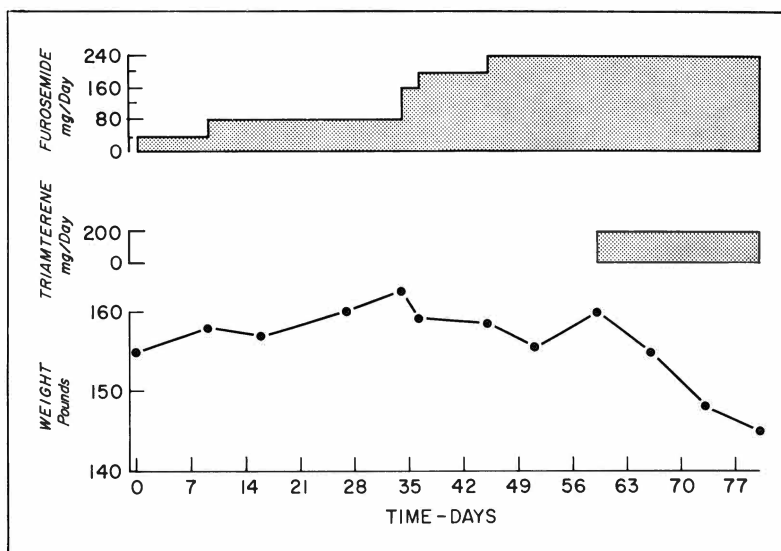


Fig. 12—The additive effect of triamterene and furosemide in a patient with diuretic-resistant chronic congestive heart failure.

* Proctor, J. D., and A. J. Wasserman, to be published.

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resis) of ethacrynic acid and the potassium sparing effect of triamterene. In this study, furthermore, ethacrynic acid effected the most favorable sodium-to-potassium excretion ratio, viz for each milliequivalent of potassium lost, ethacrynic acid caused the greatest loss of sodium (fig. 14). Stated conversely, less potassium was lost for each milliequivalent of sodium excreted with ethacrynic acid than with either hydrochlorothiazide or triamterene.

Summary

There are now a number of different classes of diuretics with different pharmacologic effects. Sev-

eral considerations dictate the choice of diuretic:

1. The responsiveness of the patient is of prime importance. If the patient is not known to be resistant to diuretic therapy, thiazides should be tried first.

2. The danger of alterations of volume and of electrolytes in the specific patient must be considered. Patients receiving digitalis will be subjected to much greater danger by the induction of hypokalemia than patients not receiving cardiac glycosides.

3. The pharmacologic effects of the specific diuretics must be understood for now the physician has available agents of differing potency, efficacy, and especially differing mechanisms of action.

References

International Furosemide Symposium. *Lasix* Dec. 5-6, 1963. Bad Homburg, Germany. Frankfurt, Germany: Farbwerke Hoechst AG; 1963.

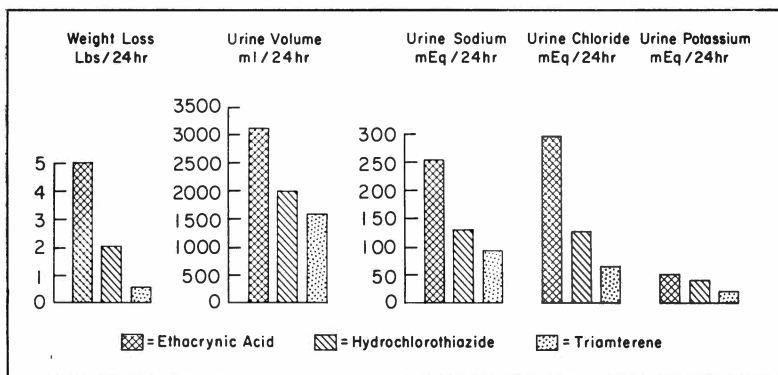


Fig. 13—Mean responses of 12 subjects with chronic congestive heart failure to ethacrynic acid, hydrochlorothiazide, and triamterene. Each subject received each diuretic (see text).

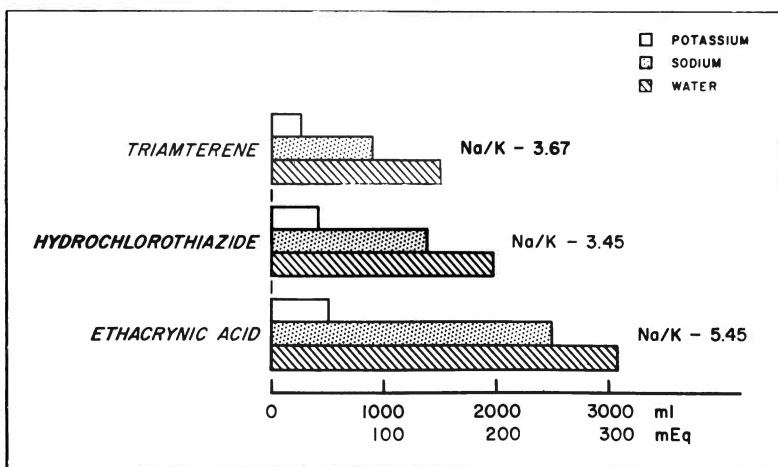


Fig. 14—Urinary sodium:potassium ratios in response to each diuretic.