Furosemide

A Clinical Evaluation of Its Diuretic Action

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Henry O. Heinemann, M.D., and John H. Laragh, M.D.

FUROSEMIDE (4 chloro-N-[2-furyl methyl]-5-sulfamyl-anthranilic acid) (fig. 1) is a new and potent diuretic compound which is effective when given either orally or parenterally. Structurally it has in common with substituted thiazides a sulfamyl-benzene grouping.

Animal studies have revealed it to be a most effective diuretic in both rats and dogs, resulting in maximum diuretic effects of up to two thirds of the glomerular filtration rate.1,2 Clearance data,3,4 micropuncture studies,5,6 and stop-flow analyses7 include sites of action in both the proximal and distal tubules, including the ascending limb of the loop of Henle. Toxicological evaluation suggests an extremely wide margin of therapeutic safety.8,9 Clinical studies to date have indicated that it is extremely potent and well tolerated.10-14

The present study was undertaken to investigate the clinical effectiveness of furosemide in various edematous states and to elucidate further the characteristics of its diuretic action.

Methods

Thirty-nine patients and seven normal volunteers were studied. Their diagnoses appear in table 1. All exhibited abnormal retention of renal sodium and water, and most had proved to be refractory to meralluride, thiazides, acetazolamide, and spironolactone administered singly or in combination.

Twenty-eight patients were studied on the medical wards of Presbyterian Hospital. The remaining 11 patients and all seven normal volunteers were admitted to our metabolism ward where they were given a diet of constant composition. Metabolic ward techniques and analytic procedures for blood and urine have been reported previously.15 In the balance studies patients had been on a constant diet for at least 4 days prior to administration of diuretics. In evaluation of the efficacy of different diuretic regimens, at least 1 day intervened between treatment days. In studies of acid-base balance the diet was of fixed composition throughout, and the diuretic was administered only after urinary excretion of hydrogen ion had been stable for 2 to 3 days. Urinary hydrogen ion excretion was calculated as the sum of the urinary excretion of ammonium plus titratable acid minus bicarbonate. Incremental changes in urine volume and excretion of sodium, potassium, and chloride were calculated by subtracting the mean amount excreted in 24 hours on the control day(s) from that excreted on the day of drug administration.

Renal clearance studies were performed on two normal volunteers on constant normal salt diets. One was studied under hydropenic conditions, the other during water diuresis. In each instance furosemide was administered orally in a single dose of 200 mg after control periods indicated a steady state of urinary flow. Procedures and calculations involved in clearance studies have been previously reported.15,16 Hydropenia was produced by deprivation of water for 15 hours and antidiuresis was assured by administering Pitressin intravenously in a priming dose of 5 μg/kg and 350 μg per hour in the sustaining infusion at 1 cc/minute. Water diuresis was induced by an oral water load and maintained by administration of amounts equal to urinary output.

Furosemide was supplied in 40 or 50-mg tablets.* The amount administered ranged from 40 mg to 1,500 mg per day. Intravenous furosemide as the sodium salt in water at pH 9.4 was supplied in 2 cc ampules containing 10 mg/cc and was administered without dilution in 10 to 20-mg doses.

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Table 1

<table>
<thead>
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<th>Diagnosis</th>
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<td>Congestive heart failure</td>
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<td>Rheumatic heart disease</td>
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<tr>
<td>Arteriosclerotic heart disease</td>
<td>11</td>
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<td>Constrictive pericarditis</td>
<td>1</td>
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<tr>
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<td>7</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Malignant effusions</td>
<td>4</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Normal subjects</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>46</strong></td>
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Results

Clinical Effectiveness and Individuality of Response

Natriuretic and diuretic responses to furosemide were impressive. Figure 2 depicts increases in urinary excretion rates of sodium, potassium, and chloride and weight loss induced over a 24-hour period in nine edematous patients by oral administration of a standard dose of furosemide. Increase in daily excretion of sodium ranged from 26 to 470 mEq and weight loss from 0.4 to 2.7 kg.

The responsiveness of different patients to a given dosage of furosemide varied considerably (figs. 2 to 4) and often could not be anticipated from the degree of responsiveness to prior diuretics. During diuresis sodium was the predominant cation accompanied by varying amounts of potassium. Chloride excretion usually exceeded the sum of sodium and potassium (fig. 2).

The effectiveness of furosemide declined when it was administered continuously (fig. 3), but intermittent administration usually restored responsiveness to its natriuretic action. Hypokalemia was often observed during diuresis (fig. 3). Ordinarily this could be controlled by administering the drug intermittently, by supplementing the regimen with oral potassium, or by the simultaneous administration of spironolactone.

Dose-Response Relationships in Edematous Patients

Doses of furosemide employed ranged from 40 mg/day in a single dose to 1,800 mg/day in three equally divided doses. A graduated increase in diuretic response was achieved by increasing doses in patients with a variety of fluid retaining states (table 2). In a normal subject (fig. 5) chloride and sodium excretion increased in nearly straight line fashion through the 300-mg dose. Significant but smaller increments in natriuresis and chloruresis were observed with doses above this level. Potassium excretion increased with increasing dosages at a much slower rate until a plateau appeared at levels in excess of 120 mg.

Special Situations

Electrolyte Abnormalities

Furosemide produced an effective diuresis in six edematous patients with marked electrolyte disturbances which included metabolic acidosis or alkalosis, hyponatremia, hypochloremia, and hypokalemia.

Azotemia

Diuresis was achieved in four patients with chronic renal disease in whom the blood urea nitrogen levels ranged from 51 to 117 mg%. However, in these patients diuretic responses were reduced and higher doses were required.

Pulmonary Edema

Furosemide was administered intravenously to three patients with pulmonary edema. A dose of 10 or 20 mg was given and then...
EFFECT OF FUROSEMIDE UPON ELECTROLYTE EXCRETION

Refractory Congestive Heart Failure

Girrhosis with Ascites

△ URINARY EXCRETION mEq/24hrs

△ WGT kg/24 hrs


Figure 2

Increments in 24-hour electrolyte excretion and weight change produced by a standard dosage of furosemide of 40 mg four times daily in nine edematous patients.

repeated in 1 hour if no response was apparent. All three patients responded with diureses ranging from 600 cc to 2,500 cc within 4 hours. This was accompanied by an impressive diminution in the clinical signs of pulmonary congestion.

Malignant Effusion

In three patients with effusion due to malignant disease (two pleural, one peritoneal) furosemide retarded fluid accumulation and diminished or eliminated the need for thoracentesis or paracentesis. One patient with lymphosarcoma and bilateral pleural effusion had required thoracentesis of 1,500 cc to 2,200 cc every 5 days for relief of dyspnea. Administration of furosemide, 200 mg two to three times daily on alternate days increased the interval between thoracentesis to 22 days.

Treatment of Outpatients

In six patients with congestive heart failure, one with cirrhosis and ascites, and one with ascites due to neoplastic disease furosemide therapy was maintained for periods of 1 to 8 months. Responsiveness had been determined in each case while the patient was hospitalized, and dosage was adjusted in the outpatient clinic according to need. The outpatient dosage schedules varied from 40 mg
twice daily to 300 mg three times daily administered intermittently on every second or third day. Edema was adequately controlled in seven of the eight patients. The eighth, an elderly lady with intractable congestive heart failure, had initially responded

with a 12-pound loss of weight. But, after discharge from the hospital, fluid reaccumulated despite continued therapy. In general, dosages required for outpatients were higher

<table>
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<th>Patient</th>
<th>Diagnosis</th>
<th>Dose (mg)</th>
<th>Weight loss (kg/24 hr)</th>
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<td>80 t.i.d.</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
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<td>120 t.i.d.</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>160 t.i.d.</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 t.i.d.</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 t.i.d.</td>
<td>1.2</td>
</tr>
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<td>P.E.</td>
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<td>200 single dose</td>
<td>1.8</td>
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<td>300 single dose</td>
<td>4.6</td>
</tr>
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</tr>
<tr>
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<td></td>
<td>80 t.i.d.</td>
<td>1.4</td>
</tr>
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<td></td>
<td>120 t.i.d.</td>
<td>2.3</td>
</tr>
<tr>
<td>K.K.</td>
<td>Nephrotic syndrome</td>
<td>80 t.i.d.</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
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<td>Cirrhosis with ascites</td>
<td>50 b.i.d.</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>200 b.i.d.</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Five patients are presented in whom the dose of furosemide was progressively increased during the course of therapy. One day intervenes between treatment days. Diuretic response is estimated by weight loss. The steady, gradual increase in response with increase in dose is illustrated.

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Dose response curve in a normal subject. Furosemide was administered every fourth day in a single dose at 7 a.m. and the urine output during the 6 hours thereafter separated from the balance of the day’s 24-hour collection and considered to represent the diuretic effect of the drug. Return to control body weight was taken as an indication that the patient had returned to a base line prior to each treatment day.

Figure 5

than those during hospitalization, perhaps due to less rigid control of sodium intake and activity.

Comparison with Other Agents and Effect of Combined Therapy

Furosemide frequently produced an effective diuresis in patients previously refractory to conventional agents. When compared with chlorothiazide (3 g/day), azetazolamide (750 mg/day), and meralluride (2 cc I.M.), furosemide, in submaximal doses, was capable of inducing considerably greater natriuresis than the maximal doses of these other agents (fig. 6). Direct comparison with ethacrynic acid indicated that in equal doses furosemide was somewhat less potent. However, in four patients with refractory edema, large doses of furosemide (400 to 1,800 mg/day) produced natriuresis of the same order of magnitude as that produced by ethacrynic acid (200 to 800 mg/day). Combination of furosemide with any of the other diuretic agents resulted in natriuretic and diuretic effects which equalled or exceeded the sum of responses observed when the drugs were administered singly.

Effect on Potassium Excretion and the Urinary Na/K Ratio

In general patients with refractory edema tended to excrete more potassium per unit of natriuresis than patients who had larger diuretic responses. This is apparent from the fact that the ratio of sodium to potassium excreted as a result of diuresis induced by furosemide was lower in patients who lost small amounts of weight during less diuresis than in those who responded with large diuresis (fig. 4). In 13 studies the ratio of the increase in urinary sodium excretion to that of potassium (ΔUNa+ / ΔUK+) ranged from 0.6 in refractory patients to 12.5 in responsive ones and averaged 3.6. Notwithstanding the favorable Na+/K ratios in responsive patients, some of this group exhibited a considerable 24-hour urinary K loss and developed hypokalemia.

Combination with Spironolactone

The addition of an aldosterone antagonist to the regimen of patients receiving furosemide potentiated the natriuretic and reduced its kaliuretic effect. In four patients with congestive heart failure (fig. 7) ΔUNa+/ΔUK- increased and a fall in the serum potassium was prevented or lessened. In two of the four patients who were more refractory to diuretics, marked potentiation of both natriuretic and diuretic effects was observed.

Effect on Acid-Base Balance

An acid-base balance study of a patient with congestive heart failure maintained on a fixed low sodium diet is illustrated in figure 8. Hydrogen ion excretion increased, especially on the first day of drug administration. This was due to increased urinary excretion of both ammonium and titratable acid. Bicarbonate excretion did not change significantly. Concomitantly blood pH rose from 7.47 to
7.50 and serum bicarbonate from 32.7 to 35.2 mEq/L.

Mild extracellular alkalosis was observed in seven patients studied similarly. Blood pH increased from a mean of 7.43 to a mean of 7.48, and serum bicarbonate increased from a mean of 26.4 mEq/L to a mean of 29.6 mEq/L. In five of these patients the pH of the urine fell during the first day of therapy; in the other two it increased. In three patients bicarbonate excretion increased slightly in association with a rather large diuresis; in the other four it remained unchanged.

Renal Clearances

Figure 9 presents results of two renal clearance studies on normal subjects, one during water diuresis and the other under maximal antidiuresis. Onset of diuresis after oral administration occurred within the first 30 minutes. Peak diuretic and natriuretic effects were reached 30 to 90 minutes after drug administration, and the action was largely dissipated in 4 hours.

During water diuresis urine flow after furosemide reached a peak of 25.7 ml/min, representing a tubular rejection fraction for water of 28.8% of the filtered load. The rejection fraction of sodium peaked at 17%. Glomerular filtration rate \( (C_{\text{f}}) \) fell slightly during peak diuresis; renal plasma flow \( (C_{\text{p}}) \) did not change significantly. The free water clearance decreased by 5.0 ml/min during peak diuresis and approached zero on the decending limb of the diuresis between 150 and 180 minutes after drug administration. Under hydropenic conditions urine flow during diuresis reached a maximum of 22.8 ml/min. The tubular rejection fraction of water peaked at 32.8%, that of sodium at 27%.
EFFECT OF ALDOSTERONE ANTAGONISTS 
ON FUROSEMIDE DIURESIS

Figure 7
Effect of aldosterone antagonists on furosemide diuresis. In four different patients spironolactone enhanced natriuretic and retarded kaliuretic effect of furosemide.

Glomerular filtration rate ($C_{fG}$) was low during control period (av. 66.6 cc/min) despite the lack of evidence of overt renal disease. However, it rose moderately during diuresis reaching a maximum of 28% above control. Renal plasma flow ($C_{PAH}$) increased markedly at the onset of diuresis but thereafter returned to or slightly above control levels. The capacity for water reabsorption ($T_{H_2O}^e$) became negative during peak diuresis and remained so until the end of the study.

Toxicity
No true toxic effects were observed. White blood cell counts, urinalyses, liver function tests including serum glutamic oxalacetic transaminase and alkaline phosphatase, and fasting blood sugar levels were unaffected. Hematocrit values frequently increased following diuresis.

Side effects included (1) hypokalemia of sufficient degree to require potassium supplementation or the addition of aldosterone antagonists in eight of 21 patients, (2) transient increase in blood urea nitrogen to levels over 30 mg% (14/26), (3) asymptomatic hyperuricemia (levels greater than 5.5 mg%) (11/16), (4) anorexia and nausea in two, (5) hepatic precama following a 1.4 kg diuresis in a patient with severe liver disease, (6) occasional postural hypotension following massive diuresis, and (7) hyponatremia and

Figure 8
Effect of furosemide on urinary acid excretion in a patient with congestive heart failure.

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PLASMA

URINARY EXCRETION

NH$_4^+$ 100
mm/da 50

TA 25
mEq/da 0

CO$_2$ 25
mm/da 0

pH 7.0
6.0
5.0

H$^+$ 50
mm/da 0

WGT 60
kg 55

FUROSEMIDE 50 qid

DAYS

5

0

Pt. M.R.65 D
ASHD with CHF

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Indeed, the combination of furosemide with either thiazides or carbonic anhydrase inhibitors produced unusually beneficial effects which at times appeared more than additive.

The rapidity of onset of its diuretic action, 3 to 5 minutes when administered intravenously, and less than 30 minutes when administered orally, makes furosemide useful in the treatment of acute situations such as pulmonary edema. The relatively brief duration of its natriuretic action, 1 to 2 hours when given intravenously, and 4 to 6 hours when given orally, allows induction of diuresis which is easily controlled by adjustment of dose and by the frequency of administration.

Responsiveness to a given dosage of furosemide varied considerably from patient to patient. It is therefore important in initiating treatment to begin with a small dose, for example 40 mg and adjust this upward step-wise over a range of 40 to 600 mg one to three times daily until the desired response is achieved. The gradual and predictable increase in response which can be achieved with increase in dosage over an unusually broad therapeutic dose range when considered together with its unusual potency points to a broad spectrum of clinical usefulness for furosemide in the management of edematous patients.

Like other diuretics the effectiveness of furosemide diminishes with continuous administration. Intermittent therapy, when the drug was given 1 to 3 days consecutively, proved more efficacious in mobilizing edema fluid than continuous therapy and was less likely to produce electrolyte or acid disturbances. Observations in outpatients indicated that furosemide retains its effectiveness over prolonged periods and is well tolerated.

During a furosemide diuresis sodium and chloride were the predominant ions excreted. However, at times appreciable potassium excretion was also induced and hypokalemia often resulted. The hypokalemia induced by furosemide could be controlled by intermittent therapy, by the addition of potassium supplements, and by combination with an aldosterone antagonist.

This study of 39 edematous patients and of seven normal volunteers extends earlier reports of the effectiveness of furosemide as a natriuretic and diuretic agent. Our data indicate that this agent is often effective in patients refractory to other diuretics. In maximal doses the potency of furosemide approaches that of ethacrynic acid and it exceeds the potency of thiazides, mercurials or acetazolamide. Furthermore, its effects appear to add to those of the other diuretics.

Thus, the combination of furosemide with either thiazides or carbonic anhydrase inhibitors produced exceptionally beneficial effects which at times appeared more than additive.

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the advantage of potentiating natriuresis in refractory patients. 

The ability of furosemide to produce an effective diuresis in more resistant patients with a variety of electrolyte disturbances which included metabolic alkalosis, acidosis, hyponatremia, hypochloremia, hypokalemia, and azotemia is a characteristic similar to that reported for ethacrynic acid and points up the distinctly greater potency of these two newer diuretics. This characteristic of these two agents portends their special usefulness in patients with refractory or complicated edema. However, greater potency clearly increases the hazard of producing overdiuresis or iatrogenic electrolyte disturbances which develop not as toxic effects but as pharmacological consequences of excessive diuretic action. Especially during the initial phases of therapy with these drugs the patient should be carefully followed and serum electrolytes frequently checked. Stepwise increases in dosage and intermittent rather than daily therapy are advisable at least at the beginning.

Stop-flow studies suggest that the kaliuresis following furosemide occurs primarily because of an increased distal tubular secretion. The importance of endogenous aldosterone activity as a determinant of the magnitude of diuretic-induced K⁺ loss has been documented in studies of ethacrynic acid. The view that distal Na⁺/K⁺ exchange induced by furosemide is likewise augmented by a secondary or underlying increase in aldosterone secretion is suggested by (1) the increased tendency for hypokalemia to occur during diuresis in those clinical situations characterized by elevated aldosterone secretion such as cirrhosis or refractory cardiac edema and (2) by the ability of spironolactone to increase the Na⁺/K⁺ ratio during furosemide diuresis. The occurrence of hypokalemia in patients, despite a favorable urinary Na⁺/K⁺ ratio, suggests that the magnitude of the sodium load delivered to ion exchange sites in the distal nephron during a furosemide diuresis is another major factor determining the amount of K⁺ loss induced by the drug.

Acid-base balance studies indicate that the extracellular alkalosis following furosemide administration results both from an increased total hydrogen ion excretion, most prominent on the first day of drug administration, and from potassium loss. The drug increased the excretion of both titratable acidity and ammonium, but bicarbonate excretion was little affected, thus verifying that furosemide has little or no carbonic anhydrase-inhibiting activity. The unusual potentiation of furosemide diuresis by carbonic anhydrase inhibitors supports this view.

Renal clearance studies failed to indicate any consistent effect of oral furosemide on renal hemodynamics, a finding which differs from the significant increases in filtration rate and renal blood flow reported by others when the drug was given intravenously. During maximal water diuresis administration of 200 mg of furosemide to our normal volunteer resulted in a tubular rejection of water of 28.8% of glomerular filtrate and under maximal antidiuresis 32.8%. The respective fractions of filtered sodium excreted during diuresis in these studies were 17% and 27%.

Vorburger, in administering the drug intravenously to patients with renal functional impairment, found tubular rejection of water to reach 60% and that of sodium 48% of the filtered load. Since the extent of these natriuretic and diuretic effects exceeds what would be expected (according to current concepts) to result from inhibition of sodium reabsorption in the loop of Henle and distal tubules, a prominent site of action in the proximal tubule is implied. That both C_H₂O and T_H₂O decreased during furosemide diuresis agrees with findings of Buchborn and Anastasakis and Suki and associates and points to a site of action in the ascending limb of the loop of Henle as well as in more cortical diluting segments of the distal tubule. Hence furosemide appears to differ in its mode of action from thiazide diuretics which have been demonstrated to inhibit C_H₂O but have no effect on T_H₂O. Micropuncture studies and stop-flow analyses suggest that furosemide has effects on both the proximal
and distal nephron, and Hook's observation in dogs that furosemide abolishes the normal medullary sodium gradient lends further support to an effect on the loop of Henle.

In dogs furosemide is capable of increasing the saline diuretic response to maximal doses of hydrochlorothiazide but to a degree which is less than additive. When superimposed on a maximal ethacrynic acid diuresis, furosemide produced only small, inconsistent increases in sodium excretion. These results suggest that furosemide has sites of action additional to those of hydrochlorothiazide but similar to those of ethacrynic acid. In our study the fact that furosemide was able to produce a significant increase in the saline and diuretic responses to ethacrynic acid when administered concomitantly with it can probably be attributed to the submaximal doses of both agents employed.

Chloride excretion after furosemide always exceeded that of sodium in both the clearance and balance studies. This might suggest a primary action of the drug to block chloride reabsorption. While this hypothesis cannot be excluded, the facts that sodium plus potassium outputs exceeded chloride in many studies and that K+ and H+ excretions were accelerated by the drug, and the lack of any precedent for primary chloride inhibition by diuretics make it seem far more likely that furosemide blocks sodium reabsorption.

Primary inhibition of sodium transport in the proximal and distal nephron, interference with passive chloride reabsorption as a consequence of the effects on sodium, and subsequent exchange of some of the rejected sodium for potassium and hydrogen ions would explain the pattern of urinary excretion observed.

Summary

The physiological effects of furosemide, a new diuretic agent chemically related to thiazide diuretics, have been evaluated in seven normal subjects and in 39 patients with edema of varied origin.

The compound exhibited an unusually broad dose-response curve so that increasing diuresis could be induced with oral doses of from 40 mg once daily to 600 mg three times daily. At the higher dosages furosemide was significantly more effective than conventional thiazide diuretics and exhibited an order of potency which can be achieved with ethacrylic acid.

In many of its diuretic properties furosemide resembled thiazide agents. The natriuresis and diuresis which it produced was associated with a disproportionate loss of chloride and potassium and the consequent production of degrees of hypokalemic alkalosis.

However, physiological studies indicate that furosemide is qualitatively and quantitatively more similar to ethacrynic acid than to thiazide agents. Thus, furosemide, like ethacrynic acid and unlike thiazide diuretics acted to interfere with both urinary concentration (TNa2O) during antidiuresis and to block urinary dilution (CNa2O) during water diuresis. It also caused a negative urinary hydrogen balance during diuresis.

The data suggest that furosemide acts to block sodium chloride reabsorption in the ascending limb of Henle's loop and in more cortical distal diluting segments. The magnitude of its effects suggests that it also may interfere with proximal sodium chloride reabsorption. Ion exchange sodium reabsorptive mechanisms appear unaffected and become overactive during drug administration thereby accounting for the observed increases in potassium and hydrogen ion excretions.

Because of its properties furosemide was especially useful intravenously as an adjunct in the treatment of acute pulmonary edema and for oral maintenance therapy in the treatment of difficult or refractory edematous patients, many of whom exhibit associated electrolyte derangements or azotemias. In these difficult situations, for maximum diuresis and to avoid problems associated with K+, H+ and Cl- depletion, intermittent therapy added to a maintenance schedule which utilizes aldosterone antagonists or chloride and potassium supplements appears advisable.

Furosemide, also like ethacrylic acid, was capable of adding to the natriuretic action of
all other types of diuretic agents. This observation provides additional evidence for the existence of a number of different tubular transport processes located at different sites in the nephron which can participate in sodium conservation.

References
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