

EXHIBIT A

DRUG BULLETIN: COUNTY OF LOS ANGELES, DEPARTMENT OF HOSPITALS

[No. 50, Los Angeles County General Hospital Therapeutics Committee, May 25, 1967]

FUROSEMIDE (LASIX, HOECHST CO.)

Furosemide, a monosulfamylanilic acid derivative, is a non-thiazide diuretic quite similar in potency and mode of action to ethacrynic acid. In maximally effective doses, furosemide is probably 8 to 10 times as potent as thiazides in increasing the excretion of sodium (1). In most cases potassium excretion is slight in relation to the natriuretic effect. Because of its mode of action, there is a strong tendency toward fluid and electrolyte disturbances, especially hypovolemia, hypokalemia, and hypochloremic alkalosis. In contrast to mercurial diuretics which lose effectiveness when alkalosis appears, furosemide—like ethacrynic acid—continues to be effective and may augment the electrolyte disturbance. To provide a safe diuresis, rapid decrease in plasma volume must be avoided, alkalosis must be prevented, and potassium balance must be maintained.

Action of furosemide: The biochemical basis of action is not known. Furosemide probably inhibits the reabsorption of sodium and water in the proximal tubules and the loop of henle and may also have some effect on the distal tubule. Sodium reabsorption may be decreased by as much as 30% (2). During maximal diuresis with furosemide, urine output may reach $\frac{1}{3}$ of the glomerular filtration rate (3). Chloride is also excreted in large amounts and bicarbonate is retained; this may lead to hypochloremic alkalosis (4). The amount of potassium loss is variable, but is usually more marked in patients with cirrhosis of the liver.

Effect of furosemide with other drugs

Furosemide has an effect similar to thiazides in lowering blood pressure and potentiates the hypotensive effect of antihypertensive agents. It decreases the arterial responsiveness to pressor amines and enhances the effect of tubocurarine.

Maximal diuresis with thiazides can be enhanced by the administration of furosemide, but maximal diuresis with furosemide is not altered by adding thiazides. Robson concluded that there was no advantage in combining thiazides with furosemide (3). However, the administration of spironolactone with furosemide in patients where there is danger of hypokalemia seems to be of benefit.

Use of furosemide

Because of its potency, this drug should be used with caution. Furosemide is particularly useful when an agent with greater diuretic effectiveness than the thiazides is needed for patients with refractory edema. Furosemide is effective in the presence of depressed glomerular filtration, acidosis, alkalosis, and hypoalbuminemia (5). This drug has been used successfully in patients with renal insufficiency and the nephrotic syndrome (5, 6) but should not be used when the patient is anuric.

When used in the management of ascites due to cirrhosis of the liver, special care must be taken to avoid rapid fluid depletion and electrolyte disturbances.

If excessive diuresis is avoided, furosemide may be used for the treatment of acute pulmonary edema.

Outpatients may be treated with furosemide, usually on an intermittent schedule, but the patient should be followed closely and electrolyte disturbances should be anticipated.

Contraindications to the use of furosemide: The safety of furosemide in pregnancy has not been determined. The drug is not recommended for cirrhotic patients in hepatic coma or those with severe electrolyte disturbances until the basic condition is improved or corrected. Furosemide is contraindicated in anuria. It is not recommended for the treatment of hypertension. Until further evidence of its safety is obtained, it is not recommended for children. Since furosemide enhances the effect of tubocurarine, great care should be exercised in administering curare-like drugs to patients receiving furosemide. NOTE.—It is advisable to discontinue furosemide therapy for one week prior to surgery if possible.