THE EFFECT OF FRUSEMIDE ON 'RESISTANT' OEDEMA

By Lee Swee Kok and Khoo Oon Teik

The last fifteen years saw great developments in the field of diuretics. Attempts were made to synthesize a diuretic with maximal efficiency and minimal side effects. These were met with successes of varying degrees. Sulphanilamide, acetazolamide and the thiazides were introduced. The mercurials and the aldosterone antagonists were also made available.

Recently, a new diuretic, "frusemide", was developed in the laboratories of Farbwerke Hoechst AG. This compound is 4-chloro-N-(2-furylmethyl)-5-sulphamoyl-anthranilic acid. It goes under the trade name of "Lasix".

We have had the opportunity to use frusemide in six patients whose oedema showed no response to other diuretics. This paper records some observations made in these patients when they were put on frusemide.

MATERIAL AND METHOD

During the period between September 1964 and March 1965, six patients with oedema were treated with frusemide forming part of the in-patient regime.

Of these, three (men) had congestive cardiac failure, which resulted from coronary thrombosis in two instances and mitral valvular disease in the third. Two (men) had cirrhosis of liver. One (girl) suffered from Disseminated Lupus Erythematosus. All presented with gross oedema mainly of the lower limbs and, except in one case, substantial ascitis.

All six had been treated with other diuretics (including acetazolamide, the thiazides, the mercurials and the anti-aldosterone preparations) previously (for not less than six months), but had shown little or no response.

In this study, frusemide was employed as the sole diuretic in only one instance. In the other cases, it was used in conjunction with other diuretics such as Mersalyl, Aldactone A and Chlortride. Digitalis was also given in the three cases with congestive cardiac failure.

Frusemide was given intramuscularly in three occasions, orally in one instance, and by both of these routes in two cases. The initial daily dose varied from 20 mg. to 120 mg. This was altered later according to the response in terms of body weight change and urinary output. Durations of courses ranged from eight to twenty days.

Salt restriction was exercised in all cases. However, there was no water restriction. Where the patient's general condition allowed, he was weighed daily. Records of daily fluid intake and urinary output were kept. Serum electrolytes were estimated at reasonably spaced intervals; urinary electrolyte studies were unfortunately unsatisfactory.

RESULTS

Diuresis

Good diuresis with accompanying weight loss occurred in five patients. One patient, who had gross oedema and ascites of some three years standing, showed no increase in urinary output; instead, there was a body-weight gain of approximately two pounds over a period of one week.

In the cases which responded to frusemide, diuresis began from one-half to two hours after institution of the drug. Good diuresis was reached from eight to twelve hours later in two instances; twenty-four hours in two cases; thirty-six hours in one occasion.

In all cases favourable response was observed during the administration of frusemide and urinary output was noted to diminish appreciably following withdrawal of the diuretic.

Dosage and Route of Administration

The highest dose reached in the present study was 120 mg. daily. The impression was that better response was obtained with increased dosage.

Only the oral and intramuscular routes of administration had been used in this study. The results show that there is little difference between the response obtained from one route and that from the other.

Serum electrolytes

There was appreciable drop in the serum sodium level in four cases; no change in one. One case showed slight increase in the serum sodium level.

The serum potassium estimations showed no loss of potassium following frusemide therapy

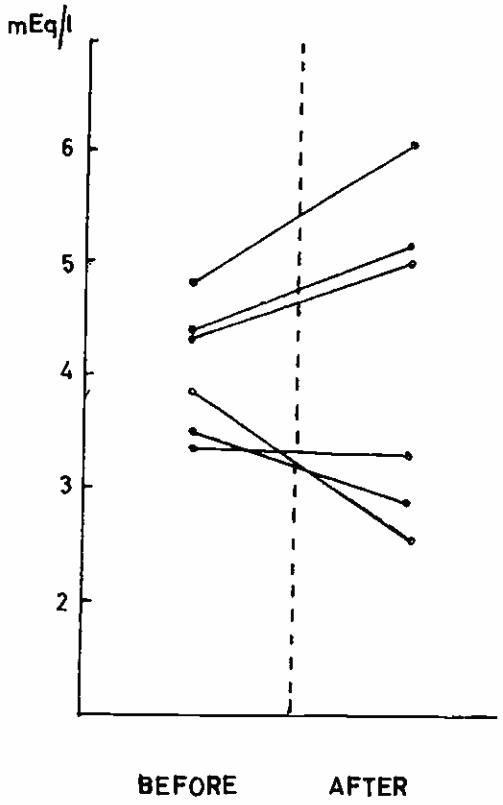

Fig. 1a. Serum Potassium Levels Before and After Administration of Lasix.

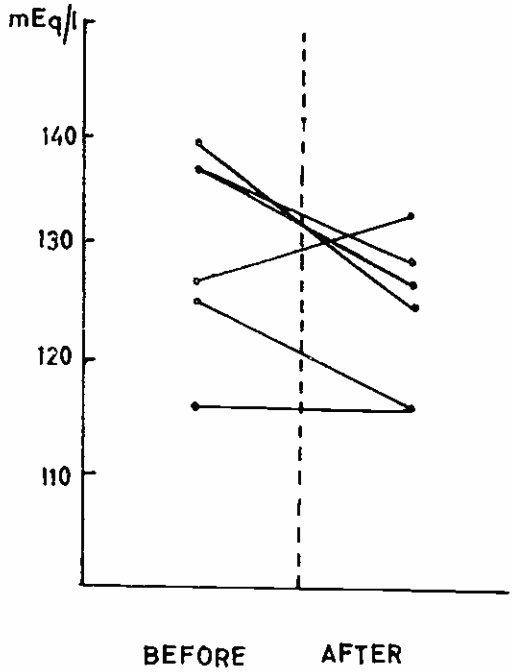

Fig. 1b. Serum Sodium Levels Before and After Administration of Lasix.

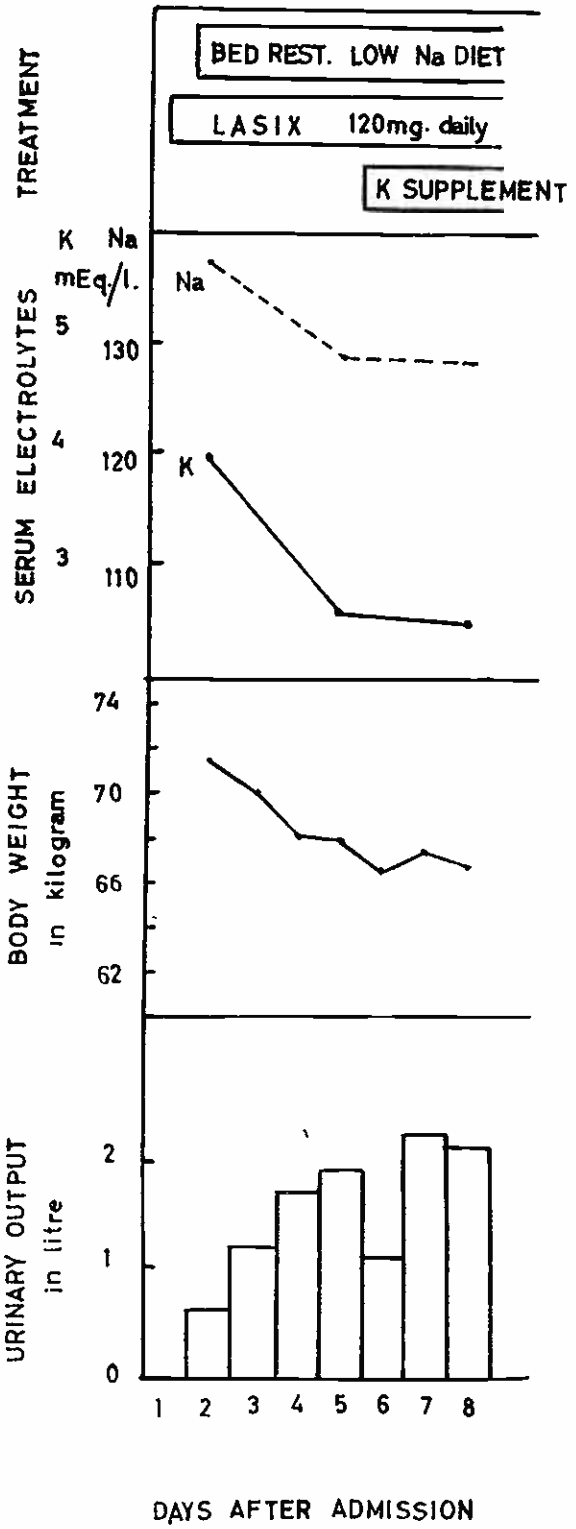

Fig. 2 Response to Lasix in a patient who had been unsuccessfully treated with other diuretics.

in four instances. There was substantial fall in serum potassium levels in two cases, requiring potassium supplementation.

Fig. 1 is a graphical representation of serum potassium and serum sodium levels before and after the administration of frusemide.

Side-effects

During this study no clinical side-effects directly attributable to frusemide were noted.

Illustrative case

Fig. 2 is a graphical record of one patient's response to frusemide. During this period the patient, a 55 year-old man who had oedema with ascites due to cirrhosis of liver, was managed with frusemide; no other diuretic was used.

DISCUSSION

In several clinical trials on patients with oedema resistant to thiazides (Kleinfelder; Vorburger), frusemide has been shown to be effective. It has been shown that some patients resistant to mercurials have also responded to frusemide (Bergstrom et al.; Larizza et al.), but not all cases do (Varel et al.; Kerr and Robson). Patients with oedema present little sodium and water to their distal tubules and would respond poorly to diuretics acting chiefly at this site. Since frusemide, in comparison with established diuretics, has been shown to act better than predicted from its dose response curve, its action at the proximal tubule is probable. In our trial, frusemide produced favourable diuresis in five out of six patients, who had shown no response to other diuretics.

It is noted that diuresis starts in one-half to two hours after oral or intramuscular administration of frusemide. Other workers (Kerr et al.; Vorburger) have reported that frusemide given intravenously initiates diuresis in as short a time as three minutes. This is a great asset when excess fluid has to be removed rapidly, *e.g.* pulmonary oedema.

Sodium loss is an important accompaniment of diuresis brought about by thiazides, as shown by the production of an urine hypertonic to plasma. More than half our cases showed sodium loss accompanying diuresis. In one case where hyponatraemia was corrected, diuresis was poor.

Potassium is generally retained during frusemide therapy, but as in two of our cases, hypokalaemia can occur; and continues despite potassium supplements (see fig. 2). This is also the experience of other workers (Robson et al.). Thus, in patients in hepatic precoma, great care must be taken to circumvent excessive electrolyte loss.

Our experience with frusemide shows that diuresis is maintained for at least 24 hours. With such a powerful diuretic, dosage may require to be spaced out, *e.g.* every other day or one or two doses in a week, depending on the response.

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