Letter to the Editor

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Furosemide-Albumin Complexes in Refractory Nephrotic Syndrome and Chronic Renal Failure

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she required ultrafiltration on two occasions. Medications included prednisone 30 mg/day, potassium chloride 10 mEq/day, the long-acting loop diuretic torsemide 60 mg/day and metolazone 10 mg/day. On examination she was awake but disoriented with a blood pressure of 130/100 mm Hg and had marked anasarca. She weighed 71 kg compared to her baseline weight (no edema) of 52 kg. Serum sodium was 132 mEq/l, potassium 2.7 mEq/l, chloride 96 mEq/l, total serum carbon dioxide 27 mEq/l, serum urea nitrogen 30 mg/dl (10.7 mmol/l), and creatinine 4.0 mg/dl (354 µmol/l). Her serum cre-

To the Editor,

Diuretic resistance is a common problem in patients with nephrotic syndrome [1]. The reasons for this may be related to several factors including impaired renal blood flow as well as effects of hypoalbuminemia and albuminuria [2]. Albumin is known to bind with high affinity to furosemide [3, 4] and appears to play a significant role in proximal tubular section of furosemide as well as other agents transported via the organic anion transport pathway [3, 5, 6]. For the patient with both renal failure as well as hypoalbuminemia diuretic resistance may become a significant problem as large doses of diuretics may be ineffective and result in ototoxicity and other adverse effects. Albumin infusions may be given, although often with little benefit and great expense [7]. In 1987 Inoue et al. [3] demonstrated that administration of furosemide complexed with albumin could significantly increase urinary output in patients with hypoalbuminemia compared to these therapies separately. In the present report we describe a patient with profound hypoalbuminemia and oliguric renal failure who was refractory to high-dose diuretics who responded to administration of furosemide-albumin complexes with a 6-fold increase in urine output.

A 33-year-old woman with a history of chronic renal failure and massive proteinuria secondary to membranous nephropathy presented to the hospital with altered mental status. She had been treated with corticosteroids but had persistent anasarca refractory to diuretics. On a hospital admission 1 month prior to this she was refractory to doses of furosemide as high as 400 mg and

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Fur-Alb

Fig. 1. Urine output during hospital course. Urine output was measured every 12 h and an hourly urine output calculated for each time period. Fur-alb = Furosemide-albumin complex administration (60 mg furosemide complexed to 12.5 g of albumin).

Atinone 1 month prior to this was 3.1 mg/dl (274 µmol/l) with a creatinine clearance of 13 ml/min. Serum albumin was profoundly diminished, being 0.3 g/dl. Serum glucose was 19 mg/dl (1.1 mmol/l) and the patient’s mental status improved following administration of 50 ml of 50% glucose solution intravenously. A prior 24-hour urine protein excretion was 3,035 mg. She was admitted and multiple doses of intravenous furosemide 160 mg and bumetanide 4 mg were administered as well as oral metolazone 10 mg without any significant increase in urinary output as illustrated in figure 1. On day 5

because of her massive fluid overload, oliguria and fear of inducing ototoxicity with repeated high doses of intravenous diuretics as well as a low likelihood of response to this therapy given her history it was decided to give a trial of furosemide-albumin complexes. These complexes were prepared by adding 60 mg of furosemide to 50 ml of 25% albumin (12.5 g), the same proportion as used by Inoue et al. [3]. The solution was infused intravenously over 15 min, and as illustrated in figure 1, a dramatic increase in urine output resulted. Urine output was only 125 ml in the 24 h preceding infusion of furosemide-albumin complexes and it increased 6-fold to 750 ml in the 24 h following infusion. The next day she again developed oliguria and an additional dose of furosemide-albumin complexes was given with a subsequent urine output of 630 ml in 24 h. The next day the patient developed upper gastrointestinal hemorrhage due to a bleeding duodenal ulcer and despite surgery she died 48 h later.

The original report of Inoue et al. [3] demonstrated for the first time that giving albumin and furosemide as a complex could significantly increase urinary output in hypoalbuminemic patients to a greater extent than an equivalent dose of albumin alone or furosemide alone. In addition, these investigators showed that analbuminemic rats had no demonstrable increase in urine output following administration of albumin alone or furosemide alone, whereas administration of furosemide-albumin complexes resulted in a marked increase in urinary output, presumably because albumin most likely plays a role in secretion of furosemide (and other organic anions) via the organic anion transporter in the proximal tubule. The series of Inoue et al. [3] included 2 patients with chronic renal failure, although the creatinine clearance for these patients was not mentioned. Serum albumin in these patients was 1.6 and 2.2 g/dl. In the present report our patient illustrates that even in the presence of advanced renal failure (creatinine clearance 9 ml/min) and profound hypoalbuminemia (0.3 g/dl), furosemide-albumin complexes may still serve a potentially useful role in increasing urinary output. Of note, our patient had such severe and refractory fluid overload that 1 month previously she had to undergo ultrafiltration as this was the only effective therapy.
It should be noted though that while the work of Inoue et al. [3] strongly suggests that hypoalbuminemia plays a role in diuretic resistance by decreasing proximal tubular secretion of furosemide, other investigators have demonstrated that urinary albumin may also play a role in diuretic resistance by binding furosemide in the tubular lumen and thus decreasing free furosemide levels [8]. Our patient had over 3 g/day of urinary protein excretion and thus we cannot exclude the possibility that in our patient diuretic resistance was in part mediated by albuminuric.

The patient in this report developed fatal upper gastrointestinal hemorrhage which was temporally related to administration of furosemide-albumin complexes. This of course raises the concern that this therapy somehow played a role in causing this ultimately fatal event. However, this patient was also receiving corticosteroids and thus it is difficult to determine at this time whether the furosemide-albumin complexes played a causative role in the upper gastrointestinal hemorrhage.

In summary, there may be a subset of patients with both profound hypoalbuminemia and advanced renal failure who may benefit from the administration of furosemide and albumin given together intravenously as a complex. This therapy may also entail less expense and a lower risk of drug toxicity as high-dose diuretic therapy may be avoided. In addition, such therapy might also diminish the need for therapies such as ultrafiltration. However, further studies may be needed to rule out any possible role of furosemide-albumin complexes in promoting gastrointestinal hemorrhage.

References


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