

CHOICE OF DIURETICS IN CIRRHOTIC ASCITES

Pages with reference to book, From 101 To 103

Huma Qureshi (PMRC Research Centre, Jinnah Postgraduate Medical Centre, Karachi.)

Ascites is one of the common complications of cirrhosis of liver, and diuretics are still the drugs of choice for its treatment. A number of diuretics are available in market but Spironolactone and Furosemide are still the most commonly used drugs either in combination or alone.

Pharmacologic studies in animals and healthy subjects have shown that furosemide (a loop diuretic) has much greater natriuretic potency than spironolactone¹. One wonders as to why is it that potent loop diuretics fail to produce natriuresis in cirrhosis? One explanation to this is that natriuretic effect of furosemide is proportional to its renal concentration,²⁻⁴ and as the renal clearance of furosemide is limited in cirrhotics, so the efficacy of the drug is also limited. Lack of natriuresis by furosemide may not be due to the failure of the drug to cause an increased distal delivery of sodium. The drug is effective in reducing sodium reabsorption in the proximal nephron, but has no effect on distal nephron.^{5,6} Thus most of the sodium not absorbed by the loop of Henle is subsequently taken up by distal and collecting tubules under the influence of spironolactone. Sodium reabsorption in distal nephron produces increased excretion of potassium^{7,8} and thus produces hypokalemia, a well known complication of loop diuretics.^{9,10}

Investigations have shown that most cirrhotics with ascites and low sodium excretion have high levels of serum aldosterone,^{11,12} so they retain sodium in convoluted, distal and collecting tubules.¹³⁻¹⁵ The efficacy of spironolactone in the treatment of cirrhotic ascites is based on the fact that hyperaldosteronism is an important factor in the retention of abnormal load of sodium. This hypothesis is further confirmed by the observation that:

(a) Increased plasma concentration of aldosterone is seen in cirrhosis with ascites.^{7,16-18} (b) Inverse relation occurs between sodium excretion and plasma aldosterone levels.¹⁸ (c) Natriuresis occurs after adrenalectomy.¹⁹ (d) A fall in plasma aldosterone level to normal occurs after spontaneous diuresis.¹⁶ (e) Direct relation exists between the dose of spironolactone required and aldosterone concentration.⁷ A dissociation between natriuresis and kaliuresis occurs during loop diuretic therapy.^{7,8}

The sole importance of aldosterone mediated retention of sodium in cirrhotics was ruled out by other workers^{17,20} and factors other than aldosterone were also thought to influence sodium retention because: Few cirrhotics with ascites have normal aldosterone levels.¹⁸ Spontaneous diuresis, occurs without any change in aldosterone levels.¹⁶ Aminoglutethimide although causes reduced synthesis of aldosterone but does not cause natriuresis.¹⁶ Placement of portocaval shunt although produces a fall in aldosterone level but does not produce spontaneous natriuresis.^{16,21}

Collecting tubule is the site of action of aldosterone^{22,23} and not the thick ascending limb and distal convoluted tubule.²² Potassium excretion or reabsorption is dependent on three, components. Firstly the potassium secretion is dependent on the luminal flow rate in the collecting tubules.²⁴ Secondly some potassium is pushed into the tubule lumen under the influence of electrochemical gradient (aldosterone mediated) for potassium.²⁵ The active transport of sodium out of the collecting tubules, makes this compartment electrically negative in respect to its outside, and it is this electrical gradient which favours potassium secretion into the luminal compartment. Moreover potassium reabsorption also occurs in the presence of luminal chloride.²⁶ Thus increased delivery of sodium and increased luminal flow rate (in response to diuretic) favours potassium secretion despite the body needs to conserve potassium.²⁷ This response is exaggerated during high levels of plasma aldosterone and renin.

About one third of cirrhotics with normal serum aldosterone levels and without renal failure respond to spironolactone alone. This is probably due to increased tubular sensitivity to spironolactone in cirrhotics with ascites. A significant increase in serum potassium without concomitant reduction of urinary potassium is seen during long and short term spironolactone therapy. The possible explanation of this observation is that aldosterone apart from influencing the external potassium balance (urinary potassium) also alters the internal potassium balance (extra and intra cellular potassium) by increasing the potassium entry into the intracellular compartment. Spironolactone when given to cirrhotics produces a reversible metabolic acidosis which induces potassium release from the intracellular to extracellular fluid compartment. It is also possible that aldosterone may raise serum potassium by decreasing the aldosterone induced potassium secretion by colon, but this hypothesis was rejected during animal experimentation.

The dose of diuretic varies from patient to patient, and the dose of spironolactone to achieve satisfactory response depends upon the degree of hyperaldosteronism. The easiest and practical way to choose which diuretic is to be given to non azotaemic cirrhotics with ascites is to collect 24hrs urinary sample after keeping the patient off all diuretics for a week. Serum and urinary electrolytes are estimated. If urinary sodium is less than 60meq/24hrs. the severe degree of hyperaldosteronism is said to be present and spironolactone 150mg in morning is recommended. After 5 days electrolytes are repeated and if urinary potassium is still less than 60 meq/24hrs then 150mg of aldactone are added in the evening dose (300mg aldactone/day). After 5 days electrolytes are repeated, if urinary sodium is now more than 60meq/day and ascites is still present then 80mg of furosemide are added to the morning dose of aldactone, and another 80mg added after 7 days if ascites is still present. Similarly if hyperaldosteronism is not present i.e. urinary sodium is more than 60meq/24hrs then 80mg of furosemide is recommended, and the dose may be doubled after 7 days if ascites persists. Potassium supplements are required during this kind of therapy, but not when aldactone is used either in combination with furosemide or alone. The dose of diuretic at which ascites is minimal is the maintenance dose, and these cases should be kept on that specific dose for a long time. In severe degree of hyperaldosteronism 500-1000mg of aldactone may be required to overcome hyperaldosteronism and achieve good response.

A combination of loop diuretics (furosemide) and distal convoluted tubule diuretics (thiazide, chlorthiazide) often produce brisk diuresis in those labelled as non responders with one or both of these drugs.^{28,29} Combination of these drugs may be used in cirrhotics, congestive cardiac failure and those with advanced renal insufficiency.

The rate of diuresis should not exceed the maximum reabsorption rate of ascites which is about 300-900ml/day.³⁰ Volume depletion and reduction in glomerular filtration rate will occur when excretion is more than absorption in the absence of peripheral oedema. Therefore in ascites without peripheral oedema a daily loss of 0.5kg is well tolerated. Fewer complications occur if the patient is not made "dry",³¹

Similar type of trial has been conducted at the PMRC research centre. Fiftyone non azotaemic cirrhotics with ascites were put on the drug trial. Dose and choice of diuretic was based on 24hrs urinary excretion of sodium. Most of the cases had severe degree of hyperaldosteronism, which was reflected by very low urinary excretion of sodium. These cases were put on 150mg of spironolactone twice daily from the day one; and furosemide was added a week later. None of the cases required more than 300mg of spironolactone to overcome hyperaldosteronism. Ascites cleared within 4-6 weeks in most of the cases. Complete withdrawal of diuretics after achieving good response resulted in recurrence of ascites in no time. To obtain long term relief from ascites the drugs should be continued for a long time and the doses may be adjusted according to the needs.

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