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Control of malignant ascites with spironolactone

Thirteen of 15 patients with malignant ascites achieved an excellent response to spironolactone, with an increase in urinary sodium excretion rates from less than 35 mEq/d before treatment to between 50 and 245 mEq/d after treatment. Plasma renin activity was raised in all of 5 patients in whom it was measured, whereas aldosterone was raised in only 3; these results are similar to those found in ascites due to cirrhosis.

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Ascites is one of the most troublesome symptoms of abdominal cancer, and treatment is often unsatisfactory. It is caused by the abnormally rapid transfer of fluid across the peritoneal membrane, compounded by blocking of the subdiaphragmatic lymphatics with tumour cells and possible activation of the renin–angiotensin–aldosterone system. Peritoneal drainage provides only temporary relief and leads to excessive protein and electrolyte loss. The LeVeen shunt (1), has been used successfully but carries the attendant hazards of possible dissemination of tumour cells, sepsis and disseminated intravascular coagulation. Intracavitary bleomycin (2, 3) has been reported to be effective in controlling malignant ascites in 36–49 per cent of patients, but pain with fever is a frequent side effect unless lignocaine is used before treatment. In 35 per cent of patients 5-fluorouracil (4) was found to be effective, except in the presence of large tumour masses or in terminal cases. Treatment of the primary abdominal tumour is seldom effective, except perhaps with deposits from a lymphoma which may respond to radiotherapy or chemotherapy. Malignant ascites is widely considered to be unresponsive to diuretic therapy (5–7), and we have found only 3 reports (8–10) in which the aldosterone antagonist, spironolactone, was beneficial.

We analyse here the response to spironolactone in 13 patients who received the drug for more than 1 week. To investigate the mechanism of this response, urinary sodium was measured before and during treatment, and in 5 patients sodium balance studies were undertaken together with the measurement of plasma aldosterone and plasma renin activity.

Patients and methods

Seventeen patients, 8 men and 9 women were studied, all of whom had tense uncomfortable ascites owing to intra-abdominal malignancy. In 13 the primary site was as follows: pancreatic ($n = 3$), ovarian ($n = 3$), colonic ($n = 4$), stomach ($n = 1$), unknown ($n = 2$), the rest having breast carcinoma.

Treatment began with 150 mg of spironolactone daily in divided doses and, if the average daily weight loss was less than 0·5 kg, the dosage was increased by 50 mg/d. Apart from the 5 patients described below, sodium intake was not restricted. Urinary sodium output and body weight were measured daily and serum electrolytes and creatinine clearance measured twice weekly. When the ascites had been controlled, patients were discharged on two-thirds of the maximum dosage that had been required. Follow-up was at monthly intervals.

Five patients were studied in more detail, with sodium balance, aldosterone and plasma renin activity measurements. Patients were maintained on a 50 mEq/d sodium diet for 14 days. On day 5, blood samples were taken for plasma aldosterone and renin activity, which were measured by radioimmunoassay (11), the patient having fasted and rested supine for 12 h beforehand.

Results

Two patients died too soon after the trial began (within 1 week) for valid assessment to be made. In 14 of the remaining 15 patients, ascites was eliminated as assessed clinically, although in one patient ascites recurred when the drug was withdrawn because of severe nausea and vomiting. In the latter patient, and in another in whom the same symptoms developed before the ascites was controlled, the nausea and vomiting could not be relieved by metoclopramide (10 mg t.d.s.) or chlorpromazine (25 mg t.d.s.). Elimination of ascites took between 10 days and 4 weeks and was associated with a mean weight loss of $4·5 \pm 2$ kg. The final daily dosage of spironolactone was 150 mg in one patient, 300 mg in 8 patients and 450 mg in 4 patients. Eight patients remained free of ascites until death at 1–4 months, and 5 remain free of ascites on maintenance therapy at between 1 and 4 months, although one of these required twice and the other three times the initial effective dose of spironolactone. There was no significant change in serum electrolytes or creatinine clearance during the observation period.

All patients showed considerable sodium retention, less than 35 mEq/d being excreted, and in 6 patients sodium excretion was less than 10 mEq/d. After beginning spironolactone treatment, there was a substantial increase in sodium excretion, more than 50 mEq/d in all patients and greater than 100 mEq/d in 10 (*Fig.* 1).

Results from 5 patients on known sodium intake confirmed net sodium retention before spironolactone and net loss after treatment. Plasma renin activity was considerably raised in all 5 patients but aldosterone was normal in 2, slightly raised in 2 and considerably raised in only 1 patient (*Table I*).

Discussion

Malignant ascites is usually associated with peritoneal metastases, but the abnormally rapid transfer into the peritoneal cavity is not only across the areas involved by tumour

Table I: *PLASMA RENIN ACTIVITY AND ALDOSTERONE LEVELS*

Case	*Primary tumour*	*Plasma renin (pmol h⁻¹ ml⁻¹)*	*Plasma aldosterone (pmol/l)*	*Urinary sodium Before treatment (mean 24 h)*	*Urinary sodium After treatment (mean 24 h)*
1	Pancreas	14·5	215	30	210
2	Stomach	12·3	598	4	126
3	Ovary	13·1	616	10	220
4	Sigmoid colon	5·32	205	20	74
5	Breast	17·0	3000	30	Died before treatment
Normal range		2·4–2·7	100–500		

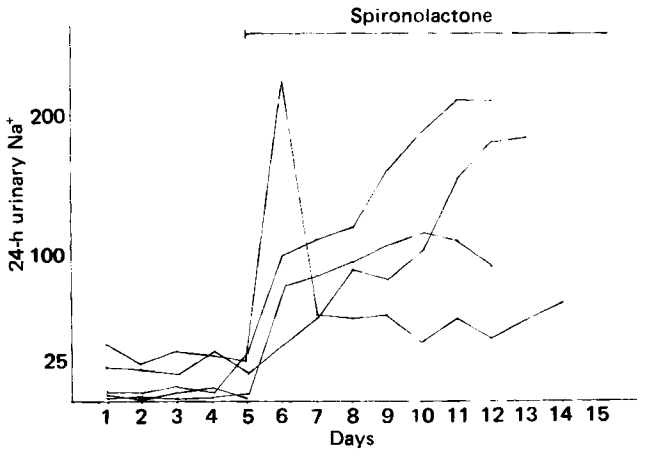

Fig. 1. *Twenty-four hour sodium excretion in 5 patients before and after treatment with spironolactone. All patients were maintained on a diet containing 50 mEq sodium per day.*

but also across apparently normal peritoneum. The latter may be mediated locally by vasoactive products (12). There is also decreased removal of excessive fluid owing to tumour infiltration of the normal drainage channels, the subdiaphragmatic lymphatic plexuses (13, 14). Dynamic studies with markers such as indian ink or ^{51}Cr-labelled red blood cells injected into malignant ascites have confirmed that fluid transfer across the diaphragm is considerably impaired (15, 16). Thus, the sodium retention we have observed is probably a secondary phenomenon consequent upon activation of the renin–angiotensin–aldosterone system which is caused by a reduction in the effective circulating extracellular blood volume. The raised plasma renin activity is consistent with this and is also found in ascites due to cirrhosis (17). It is not clear why plasma aldosterone should be low in 2 patients with high renin activity and in whom spironolactone was effective, but this situation is also found in some patients with cirrhosis and ascites where it has been attributed to increased sensitivity of the renal tubule to aldosterone (18).

Mas et al. (10) described diuretic treatment of ascites in patients with primary liver carcinoma and found a good response only in those with good renal function, but the situation is not directly comparable since all but one of their patients had underlying cirrhosis and presumably portal hypertension. Although hepatic metastases may cause portal hypertension either from a pre- or post-sinusoidal block, it is not known whether this may be primarily responsible in some cases for the development of ascites because this mechanism usually needs the addition of hypoalbuminaemia. There was no clinical evidence of portal hypertension in our patients.

Previous reports describe a total of 5 patients treated successfully with spironolactone, in 4 of whom it was given parenterally (8). Treatment of other malignant effusions and oedema was generally unsuccessful in another series in which frusemide or bumetanide was used (7), and it was concluded that these diuretics were far less effective than in the treatment of fluid overload due to cardiovascular disease.

Nausea and vomiting are uncommon side effects of spironolactone, being reported for instance in less than 2·5 per cent of patients (19). Our figure of 14 per cent suggests that patients with malignant ascites may be more susceptible. However, apart from nausea and vomiting, the lack of side effects and in particular the apparent resistance to electrolyte imbalance and renal decompensation means that long periods in hospital are not necessary, an important consideration in patients with terminal disease.

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