for epidemiological studies of blood pressure and undesirable in good clinical practice. Why the bias persisted is not clear as some reduction was observed, but it probably resulted from some doctors reading not only both the systolic and diastolic sounds but also the zero resting point to the nearest zero. The random zero device often takes 15-20 seconds to reach its nadir. Failure to allow for this delay could have prevented an accurate reading of the zero resting point and led to the biased results obtained. A recently designed modification to the device—a digital display—might reduce the bias in reading the zero point,[4] but this would be insufficient to give accurate readings as biased readings were recorded at the relevant Korotkoff sounds.

The random zero sphygmomanometer is an accurate device,[5] and it is perhaps unreasonable to expect a precision instrument intended for research to be similarly precise for normal medical care. Incorrect use of this instrument will result in incorrect readings.

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Department of Clinical Epidemiology, London Hospital Medical College, London E1 2AD
ALAN J SILMAN, MSC, MRCP, senior lecturer

Use of urea for treatment of water retention in hyponatraemic cirrhosis with ascites resistant to diuretics

Patients with cirrhosis and ascites who are resistant to normal treatment with diuretics (spironolactone with or without long loop diuretics) tend to develop hyponatraemia, which is aggravated by the hormone with urea[2] or long loop diuretics,[3] we felt it was appropriate to use urea as a complementary treatment to diuretics in patients with cirrhosis and ascites. We studied a hyponatraemic patient with resistant ascites for whom the oral administration of urea was not contraindicated. Intermittent treatment with urea induced a significant increase in diuresis that was associated with weight loss. Moreover, the hyponatraemia was corrected after treatment with urea despite the continued administration of diuretics and unrestricted water intake.

Case report

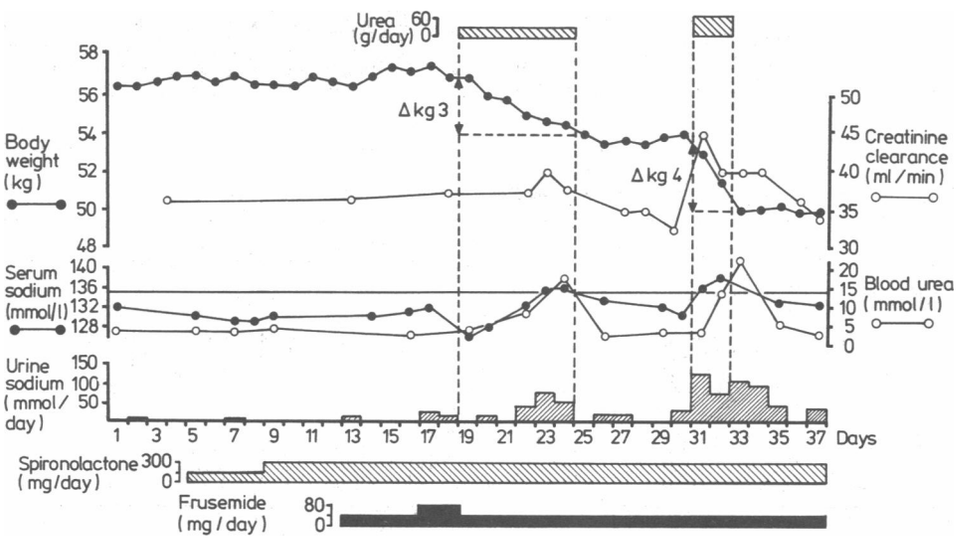
A 45 year old woman presented with alcoholic cirrhosis in icteroascitic decompensation (serum bilirubin 54 μmol/l (3 mg/100 ml) on admission) with moderate peripheral oedema. The diagnosis of cirrhosis was histologically confirmed after the removal of fluid. The patient was put on a low salt diet (10 mmol/day) and was initially given 150 mg and then 300 mg spironolactone without any change in weight, although liver function improved: serum bilirubin value decreased to 23 μmol/l (1·3 mg/100 ml). The addition of 40 mg frusemide did not increase the urine sodium output and 80 mg taken once a day exacerbated the tendency towards hyponatraemia (125 mmol(mEq)/l) (see figure). Before treatment with urea, the creatinine clearance was 30 ml/min (or 40 ml/min/1·73 m²) and serum albumin concentration was normal (34 g/l).

A daily urea intake of 30 g over six days induced a weight loss of 3 kg, an increase in serum sodium concentration (136 mmol/l) and in urinary sodium output, without any change in creatinine clearance (35-40 ml/min). When urea was stopped weight loss halted and hyponatraemia recurred (129 mmol/l). A further course of urea (60 g/day for two days) induced a weight loss of 4 kg in three days, the disappearance of any clinical features of salt retention, and an increase in serum sodium concentration (138 mmol/l) was again observed without any impairment of glomerular filtration. Arterial ammonium concentration did not change and urine volume increased from 0·6-0·8 l/day to 1·0-1·5 l/day during treatment.

Comment

Hyponatraemia associated with cirrhosis arises from renal dysfunction in water excretion. The condition can be so severe as to produce neurological symptoms, and diuretics given to treat the ascites can worsen it.

The management of hyponatraemia in an oedematous state, which has or which has not developed as a result of treatment with diuretics, is usually the restriction of water. In our patient the administration of urea induced an increased diuresis, a correction of hyponatraemia



Evolution of creatinine clearance, serum sodium concentration, blood urea concentration, urine sodium excretion, and body weight during intermittent treatment with urea.
Conversion: SI to traditional units—Serum sodium: 1 mmol/l = 1 mEq/l. Blood urea: 1 mmol/l ≈ 6 mg/100 ml.

administration of diuretics. Restricted water intake corrects the hyponatraemia, but is slow to take effect. Water retention in patients with hyponatraemia and cirrhosis has been treated with demeclocycline, in the same way as in patients suffering from inappropriate secretion of antidiuretic hormone. This treatment greatly increases the risk of renal dysfunction, however.[1] Having already treated water retention in patients with inappropriate secretion of antidiuretic without water restriction, weight loss, and no impairment of renal function. She had a creatinine clearance of 35 ml/min, and the surgical placement of a Le Veen shunt[4] seemed appropriate but was finally not required. Treatment with demeclocycline induces an increase in urinary sodium output by an unknown mechanism.[1] Our patient who was treated with urea also presented higher losses of urinary sodium. This phenomenon can result either from the effect of urea,

osmotic diuresis, or from an increase in the sodium filtered charge, which is related to the rise in serum sodium concentration.

Identical results might have been obtained with an osmotic diuresis using mannitol. A certain difference, however, exists between the two osmoles. Mannitol must be given intravenously because it cannot be absorbed intestinally. As mannitol cannot enter cells a circulatory overload may result with an attendant risk of cardiac failure, particularly if subclinical alcoholic cardiomyopathy already exists. Mannitol will transiently worsen hyponatraemia, and the combination of mannitol with frusemide has recently been reported to be nephrotoxic.[5]

In patients with a history of severe gastric disorders urea can be given intravenously. Intermittent treatment with urea could be useful in the management of some hyponatraemic and combined ascitic cirrhotic conditions without extrarenal uraemia which do not respond to diuretics.

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Department of Internal Medicine, Hôpital Universitaire Erasme, Free University of Brussels, 1070 Bruxelles, Belgium
G DECAUX, MD, PHD
P MOLS, MD

Institute of Interdisciplinary Research, School of Medicine, Free University of Brussels
P CAUCHI, MD
F DELWICHE, MD

Correspondence to: Dr G Decaux.

Intolerance of bromocriptine: is metergoline a satisfactory alternative?

Bromocriptine, a dopamine agonist, is often used to treat patients with hyperprolactinaemia. In some patients tolerance to bromocriptine is poor and the drug has to be stopped because of nausea and vomiting. Metergoline (8-*B*-carbobenzyl-ossiaminomethyl-1, 6-dimethyl-10-alpha-ergoline), a serotonin antagonist, has been used elsewhere in Europe to suppress puerperal lactation,[1] but there have been few clinical trials of metergoline in hyperprolactinaemia or normoprolactinaemic galactorrhoea. This preliminary report describes our clinical experience of using metergoline as an alternative treatment in patients intolerant of bromocriptine.

Patients, methods, and results

Metergoline was obtained on a named patient basis after informed consent was given by 14 patients (three men and 11 women) who had hyperprolactinaemia or normoprolactinaemic galactorrhoea and were intolerant of bromocriptine. Patients received an increasing dose of metergoline over two weeks, starting at 2 mg once daily and progressing to 4 mg three times daily. At monthly reassessment the dose was increased to 16 mg, 20 mg, or 24 mg in divided doses according to response, the minimum dose required to maintain the plasma prolactin concentration below 480 mU/l being given. Plasma concentrations of prolactin, urea, creatinine, cholesterol, and electrolytes, liver enzyme activities, and full blood count were measured monthly. Plasma progesterone concentration was measured on day 20, 21, or 22 if the patient was menstruating regularly.

The three men had each undergone pituitary surgery and radiotherapy for prolactinoma but still had raised plasma prolactin concentrations (mean of three estimations before metergoline in each patient 78 000 mU/l, 25 000 mU/l, and 12 000 mU/l). Plasma prolactin concentration was reduced, though not to normal, in all patients (mean of concentrations at five, six, and seven months after the start of metergoline: 5200 mU/l, 9100 mU/l, and 8210 mU/l respectively).

Three women had normoprolactinaemic galactorrhoea. Their plasma prolactin concentrations and symptoms were unchanged by metergoline. The table summarises the findings in the remaining eight women.

Side effects occurred in seven patients. Changes of mood were a common complaint: four women described depression, which lifted when metergoline was stopped, and one man described feeling detached, relaxed, and happy when the drug was started and again when the dose was increased. In three patients nausea and vomiting necessitated a reduction in dose or discontinuation of treatment. One patient developed a duodenal ulcer.

There was no unexplained change in renal or hepatic function or in the full blood count in any patient taking metergoline, and no patient developed hypopituitarism.

Comment

In this selected group of patients metergoline lowered the plasma prolactin concentration in all patients with and without identifiable tumours, but normal concentrations were not achieved. The reduction of prolactin concentration in most of the patients was modest compared with that usually effected by bromocriptine.

In six patients galactorrhoea was abolished or a regular menstrual cycle established, or both. Two women conceived while taking metergoline, although one was taking additional treatment (bromocriptine and Pergonal) after metergoline alone proved ineffective.

As metergoline acts predominantly as a serotonin antagonist[2] it might be expected to have additive or synergistic effects when combined with bromocriptine. Although it has some dopaminergic activity,[3] this is probably not the mechanism that suppresses prolactin.[4] Interestingly, the prolactin concentration in one patient was reduced further when 2·5 mg bromocriptine was added to treatment.

We emphasise that metergoline was used only in patients who were unable to tolerate bromocriptine, so the fairly high incidence of side effects may have been because these patients were unduly sensitive. As metergoline reduces the response of adrenocorticotrophic hormone to hypoglycaemia[5] hypoadrenalism should be considered in patients taking this drug. Metergoline provides satisfactory treatment for many patients unable to tolerate bromocriptine and should be useful in the management of hyperprolactinaemia either alone or combined with a small dose of bromocriptine.

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Clinical details of eight women with hyperprolactinaemia, with plasma prolactin concentrations before and during treatment with metergoline

Case No	Mean plasma prolactin (mU/l)		Tumour evident on computed tomogram	Galactorrhoea	Menstrual cycle	Comments
	Before treatment*	During treatment†				
1	1 500	890	No	Abolished	Became regular	Conceived
2	4 600	2500	No	Abolished	Periods started but irregular	
3	20 200	1020	Yes	Abolished	Menstruated once while taking metergoline	Metergoline stopped because of depression
4	1 640	Only took metergoline for one month	Yes	Continued	Remained amenorrhoeic	Depression and vomiting required reduction in dose to 4 mg twice daily but prolactin not suppressed. Unable to tolerate additional bromocriptine 2·5 mg at night
5	1 950	1330 at 3 months	Yes	Reduced	Periods became regular but did not ovulate	Metergoline stopped because of nausea and vomiting. Found to have a duodenal ulcer
6	1 800	1320	Yes	Continued	Remained amenorrhoeic	Developed depression and headache
7	55 000	1340	Yes	Reduced	Remained amenorrhoeic	With addition of bromocriptine and Pergonal to metergoline she conceived
8	135 000	1130	Yes	Reduced	Menstruated once: first time for 20 years	Had symptoms of hiatus hernia with anxiety and hyperventilation before treatment

*Mean of three measurements.
†Mean of concentrations at five, six, and seven months.