PAPERS AND SHORT REPORTS

Urea for long-term treatment of syndrome of inappropriate secretion of antidiuretic hormone

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Abstract

The efficacy of oral urea in producing a sufficiently high osmotic diuresis was tested in seven patients with the syndrome of inappropriate secretion of antidiuretic hormone. In all patients urea corrected the hyponatraemia despite a normal fluid intake. Five patients were controlled (serum sodium concentration ⩾128 mmol(mEq)/l) with a dose of 30 g urea daily, and two with 60 g daily. The patients who needed 30 g drank 1-2 l of fluid daily, while those who needed 60 g drank up to 3 l per day. No major side effects were noted, even after treatment periods of up to 270 days.

These findings suggest that urea is a safe and efficacious treatment of the syndrome of inappropriate secretion of antidiuretic hormone.

Introduction

Patients with the syndrome of inappropriate secretion of antidiuretic hormone may find the basic water-restriction treatment[1] unacceptable and suffer repeated episodes of water intoxication. A long-term treatment recommended for these patients is therefore demeclocycline,[2 3] a tetracycline derivative that produces a vasopressin-resistant polyuria and allows a large fluid intake. Harmful side effects of this drug, however, include nephrotoxicity and superinfection.[3] We recently reported alternative treatment with urea.[4] Urea decreased urinary sodium excretion in patients with hyponatraemia and induced a persistent osmotic diuresis, allowing a normal daily intake of water.[4] That report included two asymptomatic patients treated for nine days and 11 weeks, respectively,[4] and a patient with the syndrome secondary to tuberculous meningitis who was given oral urea by gastric tube.[5] We believe that the data confirm the effectiveness of urea as long-term treatment and report here an assessment of its use and drawbacks in seven new symptomatic patients who could not be controlled by simple water restriction.

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Patients and methods

During the past three years we have followed up 12 patients with hyponatraemia associated with a chronic syndrome of inappropriate secretion of antidiuretic hormone. Criteria for the diagnosis were as described.[1] Seven patients could not tolerate the strict regimen of water restriction alone (500 ml/day), so that their serum sodium concentrations remained uncontrolled. We therefore arbitrarily considered that patients whose serum sodium concentrations remained below 125 mmol(mEq)/l after five days of water restriction were candidates for treatment with urea. Of the seven patients, three had an organic brain disease and four an inoperable oat-cell carcinoma. Chemotherapy relieved the syndrome of inappropriate secretion of antidiuretic hormone in only two patients, in whom urea was stopped.

A 99% pure crystalline urea powder was prescribed as 30 g doses in small bags. Each dose was dissolved in 100 ml water with 15 g antacid (Maalox), and two patients added fruit syrup to improve the taste. The treatment was taken once daily, usually after lunch. Patients were taking a free salt diet and were asked not to drink more than 2 l a day. During the first week of treatment a blood sample was drawn daily immediately before the next dose of urea for measurement of osmolality and electrolyte, creatinine, and urea concentrations. These values were also usually measured in 24-hour urine collections. After discharge from the hospital six patients had these measurements repeated once a week and one every two weeks.

Paired Student's *t* tests were used to evaluate differences in values between basal and treatment periods.

Results

Table I shows the differences between the pretreatment and treatment periods after one week. Only two patients needed 60 g urea daily to obtain serum sodium concentrations exceeding 128 mmol/l. These patients drank 2-3 l daily, whereas the five patients who needed only 30 g urea had a fluid intake of 1-2 l daily. The blood urea concentrations remained normal in these five patients. Serum creatinine concentrations did not differ from pretreatment values, and there was generally an increase in urine osmolality. Clinical benefit was evident in all patients: all symptoms of water intoxication—for example, anorexia, headache, confusion, and somnolence—disappeared completely during treatment, and the overall condition of

TABLE I—*Comparative data in seven patients with syndrome of inappropriate secretion of antidiuretic hormone before and during treatment with urea*

Case No	Urea dose (g/day)	Days of urea treatment	Before treatment				During treatment			
			Serum sodium (mmol/l)	Blood urea (mmol/l)	Blood creatinine (μmol/l)	Urine osmolality (mmol/kg H_2O)	Serum sodium (mmol/l)	Blood urea (mmol/l)	Blood creatinine (μmol/l)	Urine osmolality (mmol/kg H_2O)
1	60	59	116	4·1	62·0	465	141	15·0	70·0	635
2	30	270	110	3·3	70·0	600	138	7·5	53·0	720
3	30	72	115	2·5	106·0	620	133	5·0	88·0	750
4	30	25	124	5·0	88·0	450	140	6·6	88·0	600
5	30	10	120	2·0	79·0	550	132	5·0	90·0	750
6	30	30	106	4·0	62·0	407	134	8·0	80·0	622
7	60	85	116	2·6	79·0	510	138	7·5	79·0	487
Mean ± SD			115 ± 6	3·3 ± 1·0	78·0 ± 15·0	514 ± 79	136 ± 3·5	7·8 ± 3·3	78·0 ± 13·0	652 ± 95
Significance							$p < 0·001$	$p < 0·001$	NS	$p < 0·001$

NS = Not significant.
Conversion: SI to traditional units—Sodium: 1 mmol/l = 1 mEq/l. Urea: 1 mmol/l ≈ 6·0 mg/100 ml. Creatinine: 1 μmol/l ≈ 0·01 mg/100 ml.

patients was substantially improved. In all cases serum sodium concentrations fluctuated widely, 128 mmol/l being the lowest value recorded and 146 mmol/l the highest. When serum sodium concentrations were measured over periods of up to 270 days, however, all patients remained symptom free. The variations in sodium concentrations were related to fluctuations in daily fluid intake. One patient complained of transient headache after the single 30-g dose of urea, but this disappeared when the dose was divided into morning and evening doses. There were no gastrointestinal complaints when urea was taken immediately after meals.

TABLE II—*Effect of urea in hypothetical case of inappropriate secretion of antidiuretic hormone compared with normal person receiving same intake of food and fluid. (Food intake shown as amount of solute for excretion in urine)*

	Daily intake	Urinary composition	Urine volume (l/day)	Water balance (l/day)
Normal	500 mmol solute; 2 l water*	250 mmol/l	2	0
Inappropriate secretion of hormone	500 mmol solute; 2 l water*	500 mmol/l	1	+1
Inappropriate secretion of hormone treated with 30 g urea daily	500 mmol solute; 500 mmol urea; 2 l water*	500 mmol/l	2	0

*Intake minus insensible loss.
Conversion: SI to traditional units—Intake and urinary composition: 1 mmol = 1 mosmol.

Discussion

After food has been digested and absorbed and those products of digestion that can be incorporated or metabolised have been utilised several solutes (fixed cations and anions, non-protein nitrogen, etc) remain that require excretion by the kidney. Similarly, the total water content of the intake and the water derived from metabolism must be excreted either as "insensible" loss or via the urinary route. Table II shows a hypothetical patient with the syndrome of inappropriate secretion of antidiuretic hormone compared with a normal man receiving the same intake of food and fluid. If the normal daily intake of food is assumed to represent 500 mmol (mosmol) of solute destined for excretion in the urine and the urinary output of water required to maintain a zero water balance is 2 l the urine composition must be 250 mmol(mosmol)/l. If this is fixed at 500 mmol/l—as in the hypothetical patient—the water balance will be positive (+1 l). When the daily food intake of such a patient is supplemented with 500 mmol (30 g) urea the urine output will again be 2 l with a composition of 500 mmol/l and the water balance will be zero.

In all but one of our seven patients treated with urea (table I) we observed an increase in urine osmolality once the serum sodium concentration had returned to normal. If in our hypothetical patient given urea (30 g/day) the urine osmolality increased to 650 mmol/l his urine volume would decrease to 1540 ml; this also implies that the single 30 g dose of urea is totally eliminated in urine over 24 hours. Analysis of urine composition showed that this was generally true, and in the patients taking only 30 g urea daily blood urea concentrations stayed in the normal range. When patients with the syndrome have low serum sodium values they usually have an abnormally high urea clearance[6] and eliminate a single 30 g dose in less than 24 hours. Five of our seven patients showed good control of their serum sodium concentration (128 to 146 mmol/l) with a daily dose of 30 g urea. The fluid intake of these patients fluctuated between 1 and 2 l per day. The two patients who needed 60 g urea daily did not have a higher urine osmolality than the others, which otherwise might have explained the need for higher urea doses, and actually drank much more (2 to 3 l of beer daily) and refused to take less. The only side effect recorded was slight headache in one patient, which disappeared when he took half the dose in the morning and the other half in the evening. The risk of urea treatment is hypernatraemic dehydration if the patient does not drink enough; this risk is minor if the thirst centre is intact and the patient has free access to water. Patients who do not have free access to water should have their serum sodium concentrations measured frequently.[5]

Urea has many advantages over demeclocycline: it acts immediately and may be given by mouth or intravenously to correct rapidly very low serum sodium concentrations.[4,7] Moreover, demeclocycline may be nephrotoxic[3] and predispose to superinfection; this second risk is high in patients with cancer whose immune responses have been suppressed by chemotherapy. Urea has no toxic effects in normal people, even at plasma concentrations of 32-50 mmol/l (193-301 mg/100 ml).[8] All our patients had a normal daily fluid intake during treatment with urea, and all symptoms of water intoxication disappeared. In general, if a patient with the syndrome of inappropriate secretion of antidiuretic hormone can restrict his intake of water to 1·5-2·0 l/day (which is in fact, the usual intake) he can be treated with 30 g urea daily (taken as a single dose or in divided doses).

In patients with very high urine osmolality—that is, over 900 mmol/kg H_2O—and a large fluid intake we prefer demeclocycline, which generally induces a high hypotonic urine output and allows a high fluid intake. We recently reported alternative treatment with frusemide[7] in a patient with peptic ulcer disease to whom we did not want to give oral urea. Frusemide treatment is easy to administer but necessitates dietary supplementation with salt, whereas with urea treatment salt intake must not be controlled; and the risk of hypokalaemic-hypochloraemic alkalosis induced by frusemide is avoided.

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Acute appendicitis in nine British towns

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Abstract

The incidence of acute appendicitis was compared among residents in nine towns in England and Wales, the towns having been chosen so that three were in the north, three in the central latitude band, and three in the south. Each group of three towns comprised one with "better," one with "intermediate," and one with "worse" socioeconomic conditions. The data were derived from hospital records for the years 1974-7. Hospital discharge rates for acute appendicitis were higher in the three northern towns in both sexes and all age groups. There was no consistent variation with the socioeconomic state of the towns.

The distribution of appendicitis in the nine towns differed from that of other "diseases of Western civilisation" and so weighs against the hypothesis of similar dietary influences in the aetiology of acute appendicitis and these other diseases. These findings are being followed up by dietary surveys in the towns.

Introduction

Donnan and Lambert[1] analysed rates of discharge from hospital for acute appendicitis by hospital region, using data from the one in 10 sample of discharges that constitutes the Hospital Inpatient Enquiry. They found that regional discharge rates showed some consistent differences over time—for example, East Anglia had consistently low rates. Regions, however, are large and heterogeneous geographical units, and the value of regional comparisons is therefore limited. This paper compares the incidence of appendicitis in nine county boroughs, selected to encompass the range of socioeconomic conditions and spread of latitude in England and Wales.

Methods

The method of selection of the nine towns has been described elsewhere.[2] In summary, the 83 largest county boroughs in England and Wales were classified into three equal groups having "better," "intermediate," and "worse" social and economic conditions. This classification was effected using a range of intercorrelated social and economic variables. The county boroughs were also divided into three groups according to latitude. One town was selected from each of the nine socioeconomic-latitude groupings. In the north the towns were York, Wakefield, and Preston; in the central latitude band Chester, Derby, and Stoke; and in the south Ipswich, Plymouth, and Newport.

Hospital Activity Analysis (HAA) data were obtained for each county borough from the regional health authorities. These data comprised tabulations of the numbers of patients resident in the county boroughs who had (1) been discharged from a hospital within the region during the period from 1 January 1974 to 31 December 1977, (2) been diagnosed as having acute appendicitis (ICD numbers 540, 541, eighth revision), (3) been admitted as emergencies, and (4) undergone appendicectomy (OPCS numbers 441, 444). Use of these criteria was intended to exclude patients with non-acute appendicitis.

These data, however, will necessarily be inaccurate. Several conditions mimic acute appendicitis, and a proportion of removed appendices are histologically normal.[3] Yet for various reasons in some of these cases the diagnosis of appendicitis still appears on the HAA records. For example, a surgeon may describe the appendix as appearing "slightly inflamed" and send the specimen for histological examination. If HAA coding is done before the histological report is received the patient is likely to be recorded as having acute appendicitis irrespective of subsequent histological findings.

Therefore, variations between the towns in the incidence of acute appendicitis, as calculated from HAA data, might reflect different HAA coding practices or surgical policies rather than true variations in incidence. For this reason it was necessary to correct the data by determining the proportion of removed appendices that were actually inflamed. Each town was visited and the pathology reports on appendicectomy specimens received during one year were inspected. In eight towns the year chosen was 1976; in the other town the records for 1977 were more complete than those for 1976 and were used instead. The appendices were classified into two groups according to the histology reports—namely, "inflamed," if polymorphonuclear leucocytes had been seen in the muscular layer of the appendicular wall, and "normal." The few equivocal reports were assessed by a consultant pathologist in Southampton.

In all towns except Preston the histology results were matched with the HAA listings of patients discharged during the same year. The proportion of patients coded as having acute appendicitis, according to the criteria described above, whose appendices were histologically normal was thereby obtained for each town. This figure was used to correct the HAA rates for the entire four-year period.

In Preston only 10% of removed appendices were sent for histological examination. Since these were unlikely to be representative of all removed appendices it was not possible to correct the HAA rates using histological data. An alternative method, based on the surgeons' comments, was used and is described below.

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