Thorax, 1979, **34**, 324–327

Demeclocycline in the treatment of the syndrome of inappropriate secretion of antidiuretic hormone

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ABSTRACT Fourteen patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) have been treated with demethylchlortetracycline (demeclocycline) 1200 mg daily. In 12 patients the underlying lesion was malignant. The serum sodium returned to normal (>135 mmol/l) in all patients after a mean of 8·6 days (SD±5·3 days). Blood urea rose significantly from the pretreatment level of 4·2±2·3 mmol/l to 10·1±5·1 mmol/l at ten days ($P<0·001$). The average maximum blood urea was 13·4±6·8 mmol/l. In four patients the urea rose above 20 mmol/l, and in two of these demecyocycline was discontinued because of this rise. The azotaemia could be attributed to a combination of increased urea production and a mild specific drug-induced nephrotoxicity. Discontinuation of demeclocycline in six patients led to a fall in serum sodium, in one case precipitously, and return of the urea towards normal levels. Demeclocycline appears therefore to be an effective maintenance treatment of SIADH, and the azotaemia that occurs is reversible and probably dose dependent.

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has become increasingly recognised as a treatable cause of stupor and confusion in patients with a wide variety of diseases (De Troyer and Demanet, 1976). Until recently treatment has been directed at correcting the electrolyte abnormalities by fluid restriction, which may be difficult in a confused patient (Perks *et al*, 1976), or treatment of the primary condition. Several case reports (Cherrill *et al*, 1975; De Troyer and Demanet, 1975; Perks *et al*, 1976; Perks *et al*, 1978) have suggested that demeclocycline is effective in SIADH. Demeclocycline interferes with the action of antidiuretic hormone on the renal collecting ducts and thus induces nephrogenic diabetes insipidus (Singer and Rotenberg, 1973). Recent publications (De Troyer, 1977; Forrest *et al*, 1978) have recorded the efficacy of demeclocycline in correcting hyponatraemia in SIADH. Impaired renal function has been reported in one patient during treatment (De Troyer, 1977). We report our experience of 14 patients with SIADH treated with demeclocycline and of the drug's effect on renal function.

Methods

Fourteen patients with a diagnosis of SIADH based on the criteria of De Troyer and Demanet (1976) have been treated with demeclocycline over the period 1976–8). All but two patients had inoperable malignant disease. Patient 1 had undiagnosed miliary tuberculosis, and patient 7 developed persistent hyponatraemia after a chest infection (table 1). All were treated with demeclocycline (demethylchlortetracycline), 1200 mg daily, in divided doses by mouth. Some were treated first by fluid restriction, but all were maintained on a free fluid intake as the serum sodium returned towards normal.

Serum electrolytes, urea, creatinine, osmolarity, and packed cell volume (PCV) were measured before and during treatment. In seven patients 24-hour urine collections were obtained for volume, urea, and electrolyte estimations.

The demeclocycline was discontinued in seven patients. Patient 5 died three days later from her primary disease. The remaining six patients were reinvestigated after a mean of 60 days (range 7–143) from discontinuation of demeclocycline.

The results were analysed statistically using paired *t* tests and analysis of correlation.

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Table 1 *Details of 14 patients with SIADH before treatment with demeclocycline*

Case No	*Diagnosis*	*Age*	*Sex*	*Plasma sodium mmol/l*	*Plasma bicarbonate mmol/l*	*Blood urea mmol/l*	*Serum osmolarity mosmol/kg*	*Urine osmolarity mosmol/kg*
1	Tuberculosis	62	M	118	21	6·7	262	642
2	Carcinoma bronchus	62	M	118	25	1·2	244	663
3	Carcinoma bronchus	46	F	111	—	1·0	266	418
4	Carcinoma bronchus	52	M	115	26	4·3	248	604
5	Carcinoma bronchus	81	F	118	22	1·7	257	365
6	Carcinoma bronchus	70	M	119	30	3·7	256	567
7	Pneumonia	77	F	120	33	6·7	253	671
8	Mesothelioma	56	M	119	—	5·9	252	418
9	Carcinoma bronchus	72	F	120	21	7·0	268	904
10	Carcinoma bronchus	51	M	119	—	1·7	271	870
11	Chronic lymphatic leukaemia	53	F	112	24	7·0	261	569
12	Carcinoma bronchus	44	F	111	24	2·7	251	558
13	Carcinoma bronchus	63	M	117	33	2·9	231	416
14	Carcinoma bronchus	66	F	99	31	4·5	217	602
	Mean	61		116	27	4·1	253	590
	±Standard Deviation	±11		± 6	± 5	±2·2	± 14	±154

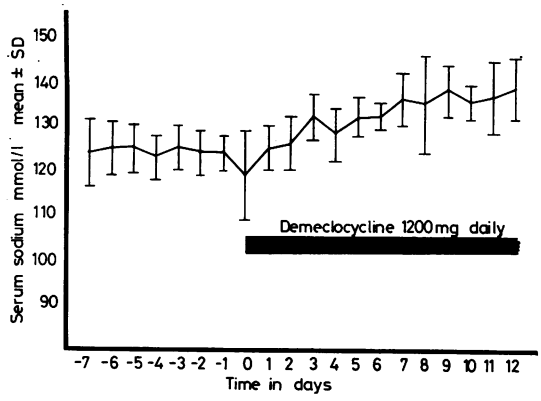
Table 2 *Comparative data before, during, and after treatment with demeclocycline.*

	No of patients	*Before treatment*	*During treatment*		*After treatment*
			At 10 days	*Minimum value*	
Serum sodium mmol/l, mean ± SD	14	118 ± 8	138 ± 7	— —	— —
Serum sodium mmol/l where demeclocycline discontinued, mean ± SD	6	122 ± 7	138 ± 6	—	125 ± 7
Urine sodium mmol/l, mean ± SD	7	54 ± 24	29 ± 21	17 ± 17	—
Urine urea serum urea ratio (uu/su), mean ± SD	9	59 ± 46	22 ± 10	19 ± 9	—

Results

During treatment with demeclocycline all patients showed an improvement in level of consciousness. The data before, during, and after treatment are summarised in table 2. The serum sodium concentration returned to normal (>135 mmol/l) in all patients after a mean of 8·6±5·3 days. The figure shows the response of the serum sodium to treatment. There was no relation between the rate of improvement of the serum sodium and the 24-hour fluid intake in the nine patients for whom adequate data were available. Both urinary sodium concentrations ($P<0.01$) and urine urea-serum urea ratios ($P<0.05$) fell significantly with treatment (table 2).

Discontinuation of demeclocycline in six patients produced a fall in serum sodium from 138 mmol/l (SD±6 mmol/l) to 125 mmol/l (SD± 7 mmol/l) ($P<0.05$). In patient 10 discontinuation of demeclocycline caused a precipitous fall in serum sodium over seven days from 138 mmol/l to 112 mmol/l with return of confusion and stupor. When the demeclocycline was restarted the serum sodium again returned to normal. He was maintained at home on demeclocycline for one year until his death from bronchial carcinoma. Details have been recorded by Perks *et al* (1976).



Response of the serum sodium to treatment with demeclocycline, 1200 mg daily, in 14 patients with SIADH.

Renal function before and during treatment with demeclocycline is shown in table 3. There was a significant rise in both blood urea ($P<0.001$)

Table 3 *Renal function before, during, and after treatment with demeclocycline*

	No of patients	Before treatment	During treatment		After treatment
			At 10 days	Maximum value	
Blood urea mmol/l, mean ± SD	14	4·2 ± 2·3	10·1 ± 5·1	13·4 ± 6·8	—
Blood urea mmol/l where demeclocycline discontinued, mean ± SD	6	4·1 ± 2·1	7·8 ± 2·1	10·4 ± 5·3	4·9 ± 4·2
Serum creatinine μmol/l, mean ± SD	13	78·5 ±20·9	106·5 ± 54·0	125·8 ± 52·5	—
Serum creatinine mmol/l where demeclocycline discontinued, mean ± SD	5	79·8 ±23·1	99·8 ± 15·5	121·0 ± 19·5	82·8 ±28·3
Packed cell volume (PCV), mean ± SD	10	0·38 ± 0·05	0·37 ± 0·05	—	—
24-hour urinary urea excretion mmol/24 h, mean ± SD	7	194 ±136	271 ± 66	404 ±127	—

and creatinine ($P<0·05$) at ten days in patients treated with demeclocycline, although the rise in the former was disproportionately greater. In the six patients in whom the demeclocycline was discontinued the blood urea and creatinine returned towards normal ($P<0·005$ and $P<0·01$ respectively). In four patients the blood urea rose above 20 mmol/l (normal range 2·5–5·8 mmol/l) on treatment and in a further four patients above 10 mmol/l. This azotaemia led to stopping demeclocycline in two patients. There was no significant relation between the rise in blood urea and the fluid intake in the nine patients in whom adequate data were available, and no change occurred in packed cell volume (PCV). There was a significant rise ($P<0·01$) in 24-hour urinary urea excretion on demeclocycline. Serial measurements of creatinine clearance in two patients (4 and 14) showed a progressive fall from 98 ml/min to 84 ml/min and from 40 ml/min to 24 ml/min respectively.

Discussion

In the 14 patients with SIADH the serum sodium returned to normal during treatment with demeclocycline, confirming the observations of De Troyer (1977) and Forrest *et al* (1978). Demeclocycline acts by inducing nephrogenic diabetes insipidus (Castell and Sparks, 1965; Roth *et al*, 1967; Singer and Rotenberg, 1973), which accounts for the fall in urine sodium concentration and urinary urea-serum ratio in our patients. At a subcellular level there is evidence of impairment of both the generation and action of cyclic adenosine monophosphate (cyclic AMP), the intracellular mediator of vasopressin (Singer and Rotenberg, 1973; Dousa and Wilson, 1974). The rate of return of the serum sodium to normal appears to be unrelated to fluid intake. Fluid restriction, therefore, may be unnecessary even in the early stages of treatment. As fluid restriction is relatively easy to manage for short periods, however, it may be used in conjunction with demeclocycline during the first few days of treatment. A free fluid intake may then be permitted. It appears from our results that the effects of demeclocycline on the serum sodium are reversible and that cessation of treatment results in a fall in serum sodium to pretreatment levels.

Azotaemia has been reported with the use of demeclocycline in congestive heart failure (Cox *et al*, 1977) and cirrhosis (Carrilho *et al*, 1977). Forrest *et al* (1978) presented data on seven patients and reported a modest rise in blood urea nitrogen. They commented that noteworthy azotaemia was not observed in any of their patients. De Troyer (1977) reported a moderate rise in blood urea and creatinine levels during treatment, but the rise was not statistically significant. Three of seven patients developed a raised urea and two a raised creatinine. In one case there was a renal metastasis and in the second no cause for the impaired renal function was found. A drug-induced nephrotoxicity was therefore invoked as a cause of this renal impairment.

In our series of 14 patients both blood urea and creatinine rose significantly on demeclocycline. The mean blood urea rose to a maximum level of more than three times the pretreatment value. These changes could not be attributed to volume depletion as there was no significant increase in PCV treatment, and in addition there was no relation between fluid intake and rate of rise in blood urea. There was, however, a significant rise in 24-hour urinary urea excretion, probably as a result of the antianabolic effect of demeclocycline (Shils, 1963). There was also a rise in serum

creatinine, although not as pronounced as the rise in urea, and, in the two patients where serial measurements were made, a fall in creatinine clearance. This azotaemia could therefore be attributed to the dual effect of excess urea production and a specific drug-induced nephrotoxicity.

The present study suggests that the adverse effects of demeclocycline on renal function are more important than previously suggested (Forrest *et al*, 1978). In four patients the blood urea rose above 20 mmol/l and in two patients the demeclocycline was discontinued as a result (with the redevelopment of hyponatraemia). Forrest *et al* (1978) used doses of demeclocycline ranging from 600 to 1200 mg daily while De Troyer (1977), as in our study, used 1200 mg daily for all patients. This higher dose may therefore be associated with an increased likelihood of impaired renal function. The effects of demeclocycline on renal function therefore appear to be both reversible and dose dependent, and it may be worthwhile to treat the condition with an initial daily dose of 1200 mg and, as the electrolytes return to normal, decrease the dose by titrating it against the serum sodium. In any case, the risk of azotaemia is a small price to pay for ease of patient management, particularly in a terminal illness.

We thank Drs M Green, K M Citron, L A Liversedge, and W van't Hoff for allowing us to report details of their patients, and Miss S Perry and Mrs B Cartlidge for secretarial help.

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