Continuous infusion of frusemide in refractory oedema

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It is well known that patients may be resistant to 'conventional' doses of frusemide, and may require a dose of up to 500 mg or more to achieve a therapeutic response (Allison & Kennedy, 1971). In our study ten patients with severe congestive cardiac failure which had proven resistant to single doses of 120 mg were treated with a continuous infusion of frusemide delivered by a constant rate infusion pump. The patients' urine volume and urine and plasma electrolyte concentrations were monitored in detail during therapy. The patients received frusemide at a mean delivery rate of 8.9 mg/h (range 4–16 mg/h). On this regime all patients experienced a vigorous diuresis: 24 h urine output 5.05 $\pm$ 3.7 l (mean $\pm$ s.d.). The mean 12 h urinary sodium excretion rose from 58.2 $\pm$ 28 mmol before therapy to 327.2 $\pm$ 202.4 mmol during the infusion. There was a similar rise in the mean 12 h potassium excretion from 29 $\pm$ 14.7 to 79.8 $\pm$ 56.6 mmol. Patients did not receive potassium supplementation during treatment, and four became hypokalaemic (plasma $K^+ < 3.5$ mmol/l). No other adverse reactions were experienced. Steady state plasma frusemide concentrations were measured during therapy in eight patients by the method of Forrey, Kimpel, Blair & Cutler (1974). In all cases the levels were low: mean 0.68 μg/ml, range 0.4–0.9 μg/ml. There was a significant correlation between the delivery rate and the obtained plasma frusemide concentration ($r = 0.79$, $P < 0.02$). Thus, these patients exhibited a satisfactory and controllable diuresis with plasma frusemide concentrations well below those thought to be necessary for a therapeutic response following administration of frusemide by a single dose (Branch, Roberts, Homeida & Levine, 1977). This proved to be a safe and effective treatment, and provides an alternative to the use of massive single doses of frusemide without the associated toxicity.

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A domiciliary study of urinary circadian rhythms in rheumatoid patients with particular reference to the effects of the time of administration of corticosteroid drugs

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There is a circadian rhythm in renal function which results in low urine flow at night and maximal urine flow in the forenoon. The loss or reversal of the normal pattern of urinary excretion often results in nocturia. This may be especially troublesome in rheumatoid arthritis patients who suffer from impaired mobility.

Many drugs alter the normal circadian rhythm of urine production and it seemed likely from a hospital based study of asthmatics that nocturia was a side-effect of corticosteroid therapy (Thomas, Coles & El-Shabourg, 1970).

Prednisolone is frequently prescribed in rheumatoid arthritis. The circadian rhymicity of urine flow rate and electrolyte excretion has been investigated in rheumatoid arthritis patients taking prednisolone at various times of the day, particularly to determine whether nocturia was more likely with a single evening dose. Patients were studied over a 3 day period on three separate occasions in the sequence, (i) after taking prednisolone as a single morning dose for at least 1 month, (ii) 4 to 6 days after changing to a

single evening dose of prednisolone and (ii) 28 days after this change.

The domiciliary collection of urine (Hillier & Knapp, 1974) was used as this avoids many of the disturbances of physiological rhythms associated with hospital admission. The subjects were asked to record the clock-time of micturition and to measure the volume of urine passed. An aliquot was retained and later analysed for sodium, potassium, calcium, creatinine and osmolality. The subjects also recorded their body temperature, weight, and assessed their joint stiffness. Six out of ten patients showed nocturia 4–6 days after the change to a single evening dose. Analysis of the urinary data (Fort & Mills, 1970) showed changes in the timing of peak electrolyte excretion rate and urine flow rate when prednisolone was taken as a single dose in the evening.

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The effect of diazepam on the threshold of the ventilatory response to CO_2

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The ventilatory response to CO_2 ($\dot{V},P_{CO_2}$ response) is measured as the linear relation between ventilation and P_{CO_2}. The slope of the line describes the sensitivity to CO_2 and the intercept on the CO_2 axis represents the threshold of the response. Recent investigations into the onset of electromyogram activity in respiratory muscles during breath-holding (Sempik, 1978) have indicated that it may be governed by the threshold of the $\dot{V},P_{CO_2}$ response and to test this hypothesis some means of changing the threshold would be useful.

There is some discrepancy in the literature as to the depressant effect of diazepam on respiration assessed by a shift of the $\dot{V},P_{CO_2}$ response. No significant respiratory depression was found by Cohen, Finn & Steen (1969) using intravenous doses up to 0.266 mg/kg. However, respiratory depression was reported by Catchlove & Kafer (1971) using intravenous doses of 0.14 mg/kg and by Utting & Pleuvry (1975) using oral doses of 5 mg.

In view of this disagreement it was decided to examine the effects of single oral doses of diazepam (5 and 10 mg) by measuring the $\dot{V},P_{CO_2}$ response of ten healthy subjects immediately before, and 1 h after the drug, using the CO_2-rebreathing method of Read (1967). Table 1 shows the results obtained. In a paired *t*-test, doses of 5 mg caused an insignificant fall in

Table 1 The mean slopes and thresholds of the $\dot{V},P_{CO_2}$ responses obtained before and after 5 or 10 mg diazepam

	Slope (l min^{-1} torr^{-1})		*Threshold (torr)*	
	mean ± s.e. means	*differences ± s.e. means*	*mean ± s.e. means*	*differences ± s.e. means*
Control	4.49 ± 0.62		45.4 ± 1.44	
		−0.82 ± 0.26		−0.1 ± 0.78
Diazepam (5 mg) $n = 7$*	3.67 ± 0.51	(*P* < 0.025)	45.3 ± 1.26	(n.s.)
Control	3.35 ± 0.48		42.7 ± 2.17	
		−0.01 ± 0.26		+2.76 ± 0.76
Diazepam (10 mg) $n = 10$	3.34 ± 0.53	(n.s.)	45.4 ± 2.36	(*P* < 0.01)

* 3 subjects were excluded from the 5 mg study because of non-linearity of the $\dot{V},P_{CO_2}$ responses.