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CONTROLLED TRIAL OF FRUSEMIDE AS AN ANTIEPILEPTIC DRUG IN FOCAL EPILEPSY

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1 The antiepileptic activity of oral frusemide (120 mg daily) was compared with that of an identical placebo in a double-blind crossover trial in fourteen patients with severe focal epilepsy who were receiving long-term therapy with established antiepileptic drugs.

2 A statistically significant reduction in the frequency of focal fits was seen with the active drug.

3 Marked drowsiness occurred in three patients during frusemide therapy, causing their withdrawal from the trial.

4 A slight, but significant, rise in serum phenobarbitone concentrations was observed during frusemide therapy, but no change was seen in serum primidone or phenytoin concentrations.

5 Frusemide significantly lowered plasma sodium and potassium concentrations, and increased plasma bicarbonate.

Introduction

Frusemide has been used successfully in the treatment of cerebral oedema, including that encountered in status epilepticus (Kramer, 1964; Doose, 1967; Dreyer, 1969; Clasen, Pandolfi & Casey, 1974). In an uncontrolled trial, Espinosa (1969) reported an antiepileptic effect of the drug given orally to patients with chronic epilepsy. In three epileptic patients, a twilight state was found to respond to parenteral frusemide, an observation which has been confirmed by one of us (S.A.) on several occasions in a single patient. Successful treatment of status epilepticus has been reported by Van der Drif (1963).

In order to evaluate these claims, we have performed a double-blind, placebo-controlled trial of oral frusemide in fourteen chronic epileptic patients whose fits had been poorly controlled by conventional drug therapy. The established therapy was continued unchanged throughout the trial. In addition, we have studied the effect of intravenous frusemide on inter-ictal electroencephalographic spikes in a further six patients. The results of this latter trial are reported separately (Ahmad & Richens, in preparation).

Methods

Ten male and four female long-stay residents at the National Hospitals–Chalfont Centre for Epilepsy were selected for the study. Table 1 gives details of the patients. In each, the history, clinical features of the fits and evidence obtained on repeated electroencephalography indicated the

Table 1 Details of patients included in the trial

Patient	*Age (years) and sex*	*Type of epilepsy*	*Anticonvulsant drug dosage (mg/day)*				
			Phenytoin	*Phenobarbitone*	*Primidone*	*Carbamazepine*	*Others*
1	32 F	Focal motor	300	180			Ethosuximide 1500; Pheneturide 400; Chlordiazepoxide 15
2	37 M	Temporal lobe	300	120			
3	37 F	Temporal lobe		90	750	600	
4	37 M	Focal motor	300	30	1200		
5	40 M	Focal motor	400		1500		
* 6	44 M	Focal motor	350	60	1000		Sodium valproate 800
* 7	29 M	Temporal lobe	400	240			Pheneturide 400
8	21 F	Temporal lobe	350		1000		
9	21 M	Temporal lobe	300		1000		
10	21 M	Focal motor	300		1000		Pheneturide 400
11	24 M	Focal motor	350	150	500		Beclamide 1500
12	23 M	Temporal lobe	300		1000	400	Ethosuximide 500; Sodium valproate 1200
13	31 F	Temporal lobe	300			600	
*14	53 M	Focal motor	300	150	1500		

* Withdrawn from trial because of adverse effects.

presence of a focal origin for the fits. In addition to focal fits, most patients had tonic-clonic fits caused by secondary generalisation of the focal discharge. House staff routinely recorded both types of fits separately on 'fit charts'. Focal fits occur frequently as they are only poorly controlled by conventional therapy. However, tonic-clonic fits are well controlled and occur so infrequently that they have been excluded from the assessment.

Frusemide was administered orally as one 40 mg tablet eight-hourly. Matching placebo tablets were used as control treatment. The fourteen patients were divided into two groups and were allocated to either treatment order using a stratified randomisation, so that the groups should have equal numbers and be balanced for sex. One group received the active treatment first and the other group the placebo. After 4 weeks of administration the treatments were crossed over and continued for a second 4-week period. The patients' established drug therapy was continued unchanged throughout the trial. The patients, the nursing staff, the clinician (S.A.) who was responsible for regular assessment of the patients, and the biochemist (L.C.) who was responsible for measuring drug levels were unaware of which treatment was being administered. The purpose of the trial was explained to the patients, and their consent to participate was obtained. Any patient suffering adverse effects was allowed to withdraw from the trial.

Blood samples were taken for plasma sodium, potassium, bicarbonate and urea estimations immediately before the trial was started and then at fortnightly intervals during the trial. These estimations were performed using the methods employed routinely in the Clinical Chemistry Department. Serum phenytoin, phenobarbitone and primidone were estimated after 2 weeks of active drug and after 2 weeks of placebo treatment. The three drugs were estimated simultaneously by the gas chromatographic method of Toseland, Grove & Berry (1972). This method does not require the formation of a derivative before chromatography.

Results

Adverse effects

Five patients (numbers 1, 2, 6, 7, 14) experienced drowsiness during the course of the trial, corresponding in each case with the administration of the active treatment. In three (numbers 6, 7, 14) this was severe enough to justify their withdrawal from the trial. Following their withdrawal, two (numbers 6, 7) recovered during the course of the following week without further drug change. The other patient (number 14), who was markedly ataxic, had to be transferred to the Regional Neurological Unit (Radcliffe Infirmary, Oxford). Here, a reduction in his phenobarbitone dosage was followed by a gradual return to his normal state over the subsequent 2 weeks. It should be noted (Table 1) that this patient was receiving primidone (1500 mg daily) and phenytoin (300 mg daily) in addition to phenobarbitone (150 mg daily).

Table 2 Effect of frusemide on the frequency of focal fits in each 4-week period

		Treatment Period			
	Patient	*Pre-trial*	*Placebo*	*Frusemide*	*Post-trial*
Group 1*	1	26	30	6	42
	2	13	12	6	14
	3	39	17	22	12
	4	8	10	0	8
	5	20	28	24	8
Group 2**	8	26	26	14	22
	9	56	30	15	35
	10	13	13	13	22
	11	28	20	8	24
	12	16	18	9	18
	13	36	20	13	31
Total		281	224	130	236

* Frusemide treatment administered first.
** Placebo treatment administered first.

Effect on focal fits

Fit frequencies during a 4-week pre-trial period, the two treatment periods and a 4-week post-trial period are recorded in Table 2. The number of fits occurring during the placebo treatment period was less than during either the pre-trial or post-trial period, but the difference was not statistically significant. Of the eleven patients who completed the trial, nine experienced fewer fits during treatment with frusemide than during administration of the placebo, one (number 3) had more fits, and the remaining patient (number 8) had an equal number during the two periods. The order of treatment did not influence the response. An analysis of variance showed that there was a significant ($P < 0.01$) difference in fit frequency between the four 4-week periods in Table 2. Patients had significantly fewer ($P < 0.001$) fits during the active treatment period than during the other periods considered.

Effect on serum levels of other drugs

Serum phenobarbitone, primidone and phenytoin levels estimated after 2 weeks of active drug or placebo treatment are given in Table 3. The three patients who were withdrawn from the trial did not complete 2 weeks of treatment and therefore no serum levels are available from them. No significant effect was found on serum phenytoin or primidone levels, but a small increase in serum phenobarbitone occurred during frusemide therapy in eight of the ten patients who were receiving either phenobarbitone or primidone. The difference between the mean phenobarbitone levels reached statistical significance at the 5% level using a matched-pairs *t*-test, but just failed to achieve this level of significance when a crossover analysis of variance was applied.

Table 3 Effect of frusemide on serum levels of phenobarbitone, primidone and phenytoin

	Serum drug level (μg/ml)					
	Phenobarbitone		*Primidone*		*Phenytoin*	
Patient	*P*	*F*	*P*	*F*	*P*	*F*
1	19	23	–	–	12	13
2	22	27	–	–	7	7
3	20	24	9	9	–	–
4	19	17	21	10	6	4
5	25	30	28	26	13	13
8	23	28	7	12	9	10
9	24	25	11	14	13	10
10	23	28	18	15	9	10
11	55	50	–	–	15	15
12	18	22	14	16	3	5
13	–	–	–	–	9	10
Mean	24.8	27.4	15.4	14.6	9.7	9.7
± s.d.	10.8	8.8	7.4	5.7	3.9	3.5
P	<0.05		NS		NS	

P Placebo treatment; *F* Frusemide treatment.

Effect on plasma electrolytes and urea

Plasma sodium and potassium concentrations were significantly reduced by frusemide therapy (from 142.6 to 140.9 mmol/l for sodium, and from 4.1 to 3.7 mmol/l for potassium, $P < 0.05$), whereas plasma bicarbonate concentration was significantly increased (from 30.1 to 32.5 mmol/l, $P < 0.05$). Plasma urea was unaffected. The patients' arterial blood pressure and body weight were recorded at weekly intervals throughout the trial, but showed no consistent change.

Discussion

Frusemide produced a highly significant reduction in the frequency of focal fits in the eleven patients who completed the trial. The average reduction was to 58% of their frequency during treatment with an identical placebo, which is an encouraging response when the drug-resistant nature of the patients' epilepsy is borne in mind. One patient with an extensive right hemisphere lesion from a depressed skull fracture did not improve, while another patient with a temporal lobe lesion deteriorated. The effect of the drug on the frequency of tonic-clonic fits was not possible to ascertain in this study because too few fits of this type occurred during the course of the trial.

Not so encouraging was the drowsiness produced in five of the fourteen patients who were admitted to the trial, requiring the withdrawal of three. The cause of this adverse reaction is uncertain although an interaction with the established antiepileptic drugs which the patients were receiving is one possibility. The significant increase in serum phenobarbitone levels, albeit small, produced by frusemide would support this suggestion. Unfortunately the serum levels in the three patients withdrawn from the trial were not monitored and it is therefore not possible to draw a firm conclusion. Eadie & Tyrer (1974) list frusemide as one of the many drugs which can cause phenytoin intoxication. Two patients with well-controlled epilepsy developed ataxia and diplopia 1-2 months after frusemide therapy had been started for premenstrual tension and ankle oedema, and serum phenytoin at this time was

noted to be in the toxic range. The patients were able to resume their usual phenytoin dose after the diuretic was withdrawn (Eadie, personal communication). Our data do not however support an interaction with phenytoin.

The precise mechanism by which frusemide reduced fit frequency in our patients remains uncertain. A direct effect on the epileptogenic focus is possible, particularly because the drug influences the distribution of monovalent ions across cell membranes (Sullivan, Tucker & Scherbenske, 1971; Askari & Rao, 1970; Wiley & Cooper, 1974), and a change of this nature is known to influence the excitability of neurones (Woodbury, 1969). Frusemide has been shown to reduce the sodium and chloride content of the brain in cerebral oedema produced experimentally in animals or caused by status epilepticus in experimental animals and in man (Kramer, 1964; Doose, 1967; Dreyer, 1969; Clasen *et al.*, 1974) and to decrease the uptake of radio-labelled sodium by the cerebral cortex when injected intraventricularly (Buhrley & Reed, 1972). Frusemide has been shown to protect rats from leptazol-induced convulsions when administered orally 4 hours before intra-peritoneal injection of the convulsant drug (Kielczewska-Mrozikiewicz, 1968). A direct action of the drug on the brain is suggested also by results of our studies of intravenous frusemide on interictal spike discharges which are published separately (Ahmad & Richens, in preparation). However, a rise in the serum level of phenobarbitone on addition of frusemide therapy might also account, at least in part, for the antiepileptic activity of the drug. A controlled study in patients receiving frusemide without phenobarbitone would be necessary to decide between these possibilities.

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References

ASKARI, A. & RAO, S.N. (1970). Drugs affecting sodium transport in human erythrocytes ghosts. *J. Pharmac. exp. Ther.*, **172**, 211-223.

BUHRLEY, L.E. & REED, D.J. (1972). The effect of furosemide on sodium-22 uptake into cerebrospinal fluid and brain. *Exp. Brain Res.*, **14**, 503-510.

CLASEN, R.A., PANDOLFI, S. & CASEY, D. Jr. (1974). Furosemide and pentobarbital in cryogenic cerebral injury and oedema. *Neurology*, **24**, 642-648.

DOOSE, H. (1967). Treatment of prolonged epileptic seizures and status epilepticus in childhood. *Mschr. Kinderheilk*, **115**, 537-538.

DRYER, R. (1969). Treatment of status epilepticus. *Med. Welt.*, **21**, 1211-1217.

EADIE, M.J. & TYRER, J.H. (1974). *Anticonvulsant Therapy, Pharmacological Basis and Practice.* Edinburgh and London: Churchill Livingstone.

ESPINOSA, L.J. (1969). The anticonvulsant activity of Lasix. *Medicina Espanola*, **61**, 280-282.

KIELCZEWSKA-MROZIKIEWICZ, D. (1968). Experimental studies on the effect of Lasix on the occurrence of Cardiazol convulsions. *Przeglad Lekarski*, **24**, 716-718.

KRAMER, G. (1964). Regulation of the water balance in cerebral oedema. *Med. Welt.*, **42**, 2238-2244.

SULLIVAN, L.P., TUCKER, J.M. & SCHERBENSKE, M.J. (1971). Effect of furosemide on sodium transport and metabolism in toad bladder. *Am. J. Physiol.*, **220**, 1316-1324.

TOSELAND, P.A., GROVE, J. & BERRY, D.J. (1972). An isothermal g.l.c. determination of the plasma levels of carbamazepine, diphenylhydantoin, phenobarbitone and primidone. *Clinica chim. Acta.*, **38**, 321.

VAN der DRIF (1963). Cited by Espinosa (1969).

WILEY, J.S. & COOPER, A.C. (1974). A furosemide-sensitive cotransport of sodium plus potassium in the human red cell. *J. clin. Invest.*, **53**, 745-755.

WOODBURY, D.M. (1969). Mechanisms of action of anticonvulsants. In *Basic Mechanisms of the Epilepsies*, pp. 647-681. Ed. Jasper, H.H., Ward, A.A. & Pope, A. Edinburgh and London: Churchill Livingstone.

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