- 16 Weitgasser H. The use of pentoxifylline ('Trental' 400) in the treatment of leg ulcers: results of a double-blind trial. *Pharmatherapeutica* 1983;3(suppl 1):143-51.
- 17 Anonymous. Dressings for leg ulcers. *Drug Ther Bull* 1986;24:9-12.
- 18 Blair SD, Wright DDI, Backhouse CM, Riddle E, McCollum CN. Sustained compression and healing of chronic venous ulcers. *Br Med J* 1988;297:1159-61.
- 19 Arenas R, Atoche C. Post-thrombotic leg ulcers: safety and efficacy of treatment with pentoxifylline (double-blind study in 30 patients). *Dermatologica. Revista Mexicana Segunda Epoca* 1988;32:34-8.
- 20 Leyh F. Therapie des Ulcus cruris venosum mit Mäusedornextrakt und Trimethylperidinchalkon. *Therapiewoche* 1988;38:2325-31.
- 21 Belcaro G, Marelli C. Treatment of venous lipodermatosclerosis and ulceration in venous hypertension by elastic compression and fibrinolytic enhancement with defibrotide. *Phlebology* 1989;4:91-106.
- 22 Mann RJ. A double blind trial of oral O, 6-hydroxyethyl rutosides for statil leg ulcers. *Br J Clin Pract* 1981;35:79-81.
- 23 Schraibman IG. The bacteriology of leg ulcers. *Phlebology* 1987;2:265-70.
- 24 Ward A, Clissold SP. Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. *Drugs* 1987;34:50-97.
- 25 James DR, Holland BM, Hughes MR, Jones JG, Wardrop CAJ. Oxpentifylline: effects on red cell deformability and oxygen availability from the blood in intermittent claudication. *Clinical Hemorrhology* 1984;4:525-31.
- 26 Angelkort B, Kieseewetter H. Influence of risk factors and coagulation phenomena on the fluidity of blood in chronic arterial occlusive disease. *Scand J Clin Lab Invest* 1984;41(suppl 156):185-8.
- 27 Knox P. Leukocyte-mediated activation of the fibrinolytic pathway and the effects of pentoxifylline. In: Mandell GL, Novick WJ, eds. *Pentoxifylline and leukocyte function*. Somerville, New Jersey: Hoechst-Roussel Pharmaceuticals, 1988:96-104.
- 28 Bertocchi F, Proserpio P, Lampugnani MG, Dejana E. The effect of pentoxifylline on polymorphonuclear cell adhesion to cultured endothelial cells. A preliminary report. In: Mandell GL, Novick WJ, eds. *Pentoxifylline and leukocyte function*. Somerville, New Jersey: Hoechst-Roussel Pharmaceuticals, 1988:68-74.

(Accepted 15 January 1990)

Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects

Jan E Carlsen, Lars Køber, Christian Torp-Pedersen, Peter Johansen

Abstract

Objective—To determine the relevant dose of bendrofluazide for treating mild to moderate hypertension.

Design—Double blind parallel group trial of patients who were given placebo for six weeks and then randomly allocated to various doses of bendrofluazide (1.25, 2.5, 5, or 10 mg daily) or placebo for 12 weeks.

Setting—General practices in Zealand, Denmark.

Patients—257 Patients with newly diagnosed or previously treated hypertension, aged 25-70, who had a mean diastolic blood pressure of 100-120 mm Hg after receiving placebo for six weeks.

Main outcome measures—Reduction in diastolic blood pressure and changes in biochemical variables (potassium, urate, glucose, fructosamine, total cholesterol, apolipoprotein A I, apolipoprotein B, and triglyceride concentrations).

Results—All doses of bendrofluazide significantly reduced diastolic blood pressure to the same degree (10-11 mm Hg). Clear relations between dose and effect were shown for potassium, urate, glucose, total cholesterol, and apolipoprotein B concentrations. The 1.25 mg dose increased only urate concentrations, whereas the 10 mg dose affected all the above biochemical variables.

Conclusion—The relevant range of doses of bendrofluazide to treat mild to moderate hypertension is 1.25-2.5 mg a day. Higher doses caused more pronounced adverse biochemical effects including adverse lipid effects. Previous trials with bendrofluazide have used too high doses.

Introduction

The use of thiazides for treating arterial hypertension has been criticised. The arguments have been that thiazides do not reduce excess mortality, do not reduce the incidence of myocardial infarction, increase known risk factors, and produce more adverse effects than previously realised. As no treatment has yet shown a clear reduction in mortality or morbidity from acute myocardial infarction interest has focused on the risk factors and adverse effects. Evidence against thiazides was substantiated by a Medical Research Council trial, which compared treatment with a fixed dose of bendrofluazide (10 mg/day) or a titrated dose of propranolol with placebo.^{1,2} There was no basis for choosing a dose of 10 mg bendrofluazide.

We investigated the relevant dose range of bendro-

fluazide for treating mild to moderate arterial hypertension as this could affect both the choice and outcome of treatment.

Methods

Selection of patients—Patients aged 25-70 presenting to general practices in Zealand, Denmark, with newly diagnosed or previously treated arterial hypertension (up to two drugs) who gave informed consent were eligible for the study.

Patients were excluded if they were pregnant or lactating; had had a myocardial infarction or stroke within the past six months; had angina pectoris; were being treated for heart failure, gout, or uncontrolled diabetes mellitus or with drugs that reduced lipid concentrations; were intolerant of bendrofluazide; had reduced kidney function (creatinine concentration >150 µmol/l); did not take 80-120% of the prescribed tablets while receiving a placebo at the start of the study.

Study design—Patients whose blood pressure was between 100 and 120 mm Hg after they had taken placebo for six weeks were randomly allocated in blocks of 10 on a double blind basis to receive placebo or bendrofluazide at a dose of 1.25, 2.5, 5, or 10 mg a day. Randomisation was performed from a list of computer generated numbers. The 10 mg dose was chosen because this was used in the Medical Research Council's trial and the 2.5 and 5 mg doses because they are recommended by the joint national committee on detection, evaluation, and treatment of high blood pressure.³ The dose of 1.25 mg was believed to represent a point on the lower part of the dose-response curve. The active tablets contained 573 mg potassium chloride and either 1.25 mg or 2.5 mg bendrofluazide (Centyl K, Leo Pharmaceutical Products). Placebo and active tablets were identical in appearance and taste. All patients received four tablets daily, two in the morning and two at lunch. Those receiving fewer than four active tablets daily were given the active tablets in the morning. Patients were assessed on an outpatient basis for four, 10, and 12 weeks after randomisation. Biochemical variables were measured before randomisation and at the end of the study; these variables included total cholesterol, apolipoprotein A I, apolipoprotein B, sodium, potassium, glucose, fructosamine, urate, and creatinine concentrations. The study was approved by the local ethical committee.

Methods of assessment—The patient's blood pressures were measured twice, in the sitting position after five

Medicon, Svanemøllevej 2,
DK-2100, København Ø,
Denmark

Jan E Carlsen, MD, senior
lecturer
Lars Køber, MD, resident
Christian Torp-Pedersen,
MD, senior lecturer

Leo Pharmaceutical
Products, Industriparken,
DK-2750, Ballerup,
Denmark
Peter Johansen, PHD, medical
adviser

Correspondence to:
Dr Carlsen.

Br Med J 1990;300:975-8

minutes' rest, with a random zero sphygmomanometer (Hawksley) and a Tricuff. Diastolic blood pressure was taken at the point where Korotkoff sounds disappeared (phase V). Three trained nurses took all the blood pressure measurements. Heart rate was assessed by counting the radial pulse. At each visit patients were asked about adverse effects. All biochemical analyses were carried out in a high quality automated laboratory (CALAB, Stockholm, Sweden).

Statistical analyses—All values are given as means

TABLE I—Demographic characteristics of 257 patients with mild to moderate hypertension

	Dose of bendroflumazide (mg/day)				
	0	1.25	2.5	5.0	10.0
No	52	50	52	52	51
No of men	23	16	17	19	28
Mean age (years)	57	60	54	57	59
Mean weight (kg)	75	75	73	79	72

TABLE II—Variation in blood pressure and heart rate in 257 patients throughout trial according to amount of drug taken. All values are means (SE)

	Dose of bendroflumazide (mg/day)				
	0 (n=52)	1.25 (n=50)	2.5 (n=52)	5.0 (n=52)	10.0 (n=51)
<i>Value at start of trial</i>					
Systolic blood pressure (mm Hg)	161.9 (1.9)	167.8 (2.6)	161.6 (1.9)	164.3 (1.8)	166.9 (2.7)
Diastolic blood pressure (mm Hg)	101.8 (0.5)	102.4 (0.6)	103.0 (0.6)	104.2 (0.9)	103.7 (0.8)
Heart rate (beats/min)	74.8 (1.0)	75.8 (1.2)	75.8 (1.5)	77.5 (1.0)	75.4 (1.0)
<i>Difference at week 4</i>					
Systolic blood pressure (mm Hg)	-0.9 (1.8)	-6.4 (2.0)	-11.3 (2.1)	-11.5 (1.8)	-11.7 (1.8)
Diastolic blood pressure (mm Hg)	-2.9 (0.9)	-7.5 (1.1)	-8.7 (0.8)	-8.1 (1.1)	-9.0 (1.0)
Heart rate (beats/min)	-1.9 (1.0)	-2.4 (1.1)	-1.8 (1.5)	-0.1 (1.3)	-0.5 (1.4)
<i>Difference at mean of 10-12 weeks' treatment</i>					
Systolic blood pressure (mm Hg)	-2.8 (1.7)	-12.7 (2.0)**	-14.3 (1.6)	-13.4 (2.0)	-17.0 (2.1)**
Diastolic blood pressure (mm Hg)	-3.5 (0.8)	-9.8 (1.0)*	-10.8 (0.9)*	-10.1 (1.1)	-10.8 (1.0)
Heart rate (beats/min)	-0.7 (1.1)	-1.2 (1.0)	-0.6 (1.3)	0.8 (1.1)	-2.5 (1.1)

* $p < 0.05$, ** $p < 0.01$, comparing weeks 10-12 with week 4.

TABLE III—Number (percentage; 95% confidence interval) of patients whose diastolic blood pressure dropped by ≥ 10 mm Hg during trial

	Dose of bendroflumazide (mg/day)				
	0	1.25	2.5	5.0	10.0
Week 4	6 (12; 4 to 23)	19 (38; 24 to 51)	21 (40; 27 to 55)	21 (40; 27 to 55)	22 (43; 30 to 58)
Mean of 10-12 weeks' treatment	6 (12; 4 to 23)	22 (44; 29 to 57)	25 (48; 34 to 62)	26 (50; 36 to 64)	27 (53; 39 to 67)

TABLE IV—Mean (SE) values of biochemical variables at beginning of trial and change after 10 weeks' treatment

	Dose of bendroflumazide (mg/day)					p Value
	0.0	1.25	2.5	5.0	10.0	
Potassium (mmol/l):						
Baseline	4.36 (0.05)	4.27 (0.06)	4.25 (0.05)	4.32 (0.06)	4.33 (0.05)	
Change at 10 weeks	0.09 (0.06)	-0.16 (0.06)	-0.20 (0.05)*	-0.33 (0.06)***	-0.45 (0.06)***	
Urate (μ mol/l):						
Baseline	300.0 (11.0)	314.0 (11.2)	324.0 (10.7)	324.0 (11.3)	322.0 (9.7)	
Change at 10 weeks	-5.0 (5.3)	19.0 (6.1)**	29.0 (7.7)***	63.0 (14.3)***	68.0 (7.5)***	
Creatinine (μ mol/l):						
Baseline	85.0 (2.4)	78.6 (1.9)	81.5 (1.8)	79.0 (2.4)	86.4 (3.2)	
Change at 10 weeks	-2.7 (1.6)	2.4 (1.6)*	2.5 (1.4)*	2.3 (3.0)	3.8 (1.4)**	0.068
Glucose (μ mol/l):						
Baseline	4.88 (0.10)	5.31 (0.19)	4.77 (0.12)	5.10 (0.10)	4.96 (0.11)	
Change at 10 weeks	-0.08 (0.09)	-0.19 (0.11)	0.14 (0.10)	0.04 (0.10)	0.27 (0.15)*	0.008
Fructosamine (mmol/l):						
Baseline	2.08 (0.03)	2.12 (0.04)	2.08 (0.03)	2.07 (0.03)	2.06 (0.03)	
Change at 10 weeks	-0.02 (0.03)	-0.01 (0.04)	0.03 (0.03)	0.03 (0.03)	0.06 (0.04)	0.066
Cholesterol (mmol/l):						
Baseline	5.99 (0.15)	6.53 (0.15)	5.86 (0.16)	6.03 (0.13)	5.84 (0.17)	
Change at 10 weeks	-0.06 (0.09)	-0.03 (0.11)	0.00 (0.09)	0.12 (0.10)	0.25 (0.09)*	0.01
Apolipoprotein A I (g/l):						
Baseline	1.38 (0.02)	1.36 (0.02)	1.34 (0.03)	1.39 (0.03)	1.30 (0.03)	
Change at 10 weeks	0.01 (0.02)	0.02 (0.02)	0.02 (0.02)	0.02 (0.02)	0.01 (0.02)	0.999
Apolipoprotein B (g/l):						
Baseline	1.23 (0.03)	1.39 (0.04)	1.26 (0.04)	1.21 (0.03)	1.23 (0.04)	
Change at 10 weeks	0.02 (0.02)	-0.01 (0.03)	-0.07 (0.03)*	0.04 (0.03)	0.07 (0.03)	0.02
Triglyceride (mmol/l):						
Baseline	1.48 (0.17)	1.62 (0.12)	1.55 (0.18)	1.93 (0.23)	1.38 (0.11)	
Change at 10 weeks	-0.13 (0.15)	0.00 (0.10)	0.39 (0.12)*	-0.05 (0.22)	0.14 (0.09)	0.53

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with placebo.

p Value denotes significance between the change and the dose of bendroflumazide.

and standard errors (SE). Discrete variables were compared with a χ^2 test and continuous variables, which were checked for normal distribution and equal variance, with Student's t test. Significance was accepted if type I error risk was below 5% (two sided).

Sample size—The sample size was calculated according to the methods of Dunnett.⁴ We planned to have equal numbers in each group. The minimal relevant difference was considered to be 5 mm Hg and the standard deviation estimated to 7 mm Hg. With type I and type II error risks of 5% and 10% we needed 50 patients in each group.

Results

Table I shows the demographic data on the patients. There were no large differences among the groups.

Table II shows the changes in blood pressures during the study. The diastolic blood pressure decreased significantly in all groups: by 3 mm Hg in the placebo group and 10-11 mm Hg in the actively treated groups. The dose of bendroflumazide did not significantly affect the reduction in diastolic blood pressure. The mean difference in diastolic pressure between the 1.25 mg and 2.5 mg doses was -1.2 mm Hg (95% confidence interval -3.9 to 1.5) at week 4 and -1.0 mm Hg (95% confidence interval -3.7 to 1.7) at the end of the trial.

The systolic blood pressure in the placebo group did not change, although in the treated groups it decreased by 13-17 mm Hg with no significant difference between groups. The mean difference in systolic pressure between the 1.25 mg and 2.5 mg doses was -4.9 mm Hg (95% confidence interval -10.6 to 0.8) at week 4 and -1.6 mm Hg (95% confidence interval -6.6 to 3.4) at the end of the trial. Changes in blood pressure occurred slowly. Only a partial effect was present for both the systolic and diastolic pressures after four weeks' treatment. The heart rate did not change in any group.

We defined responders as patients whose diastolic blood pressure decreased by ≥ 10 mm Hg (table III). The number of responders increased from week 4 to the end of the trial in all groups receiving bendrofluazide. Roughly half of the actively treated patients were responders.

Table IV shows the baseline biochemical values and the changes that occurred during the study. No correlation existed between the dose of bendrofluazide and the change in apolipoprotein A I and triglyceride concentrations. Marginal correlations were found with creatinine and fructosamine concentrations, and highly significant correlations with glucose, total cholesterol, potassium, apolipoprotein B, and urate concentrations. The lowest doses of bendrofluazide (1.25 mg and 2.5 mg) significantly increased creatinine and urate concentrations, and the 2.5 mg dose also decreased potassium concentrations. Changes induced by the two highest doses were more pronounced: the 10 mg dose significantly changed potassium, urate, creatinine, glucose, and total cholesterol concentrations.

Nine patients were withdrawn from the study because of subjective adverse effects: one from the group receiving 5 mg/day and two in each of the other groups. Forty seven patients experienced adverse effects (table V), and in 21 of them the effects were typical of thiazides. We found no relation between either biochemical changes or subjective adverse effects and changes in blood pressure. The response to treatment was not affected by gender.

TABLE V—Adverse effects experienced by patients participating in trial of bendrofluazide

	Dose of bendrofluazide (mg/day)				
	0	1.25	2.5	5.0	10.0
Attack of gout			1		
Impotence			1		1
Constipation					4
Leg pain			1		3
Headache	4	1	1		
Dry mouth			2	1	3
Dizziness		1	3	1	4
Frequent voiding of bladder					3
Palpitations				3	
Others	5	6	5	7	6
Total	9	8	14	12	24

Discussion

Drug trials should not be conducted without knowing the relevant dose.⁵ Hypertension is treated to prevent mortality and morbidity, and an ideal dose-response study should establish the relation between the dose and the reduction in mortality and morbidity. Obviously, such studies are not feasible so the relation between the dose and the antihypertensive effect is usually studied. The dose that lowers the blood pressure most does not necessarily have the greatest effect on mortality and morbidity.

When deciding on the dose for clinical use it is necessary to strike a balance between unwanted and wanted effects. Several antihypertensive drugs have been introduced with too high doses. Both the number and the severity of adverse effects can be reduced by using smaller doses without affecting the efficacy. Thiazides are used to treat several conditions, and the optimal dose for each condition is not the same, as was assumed in early studies.^{6,7}

Knowledge of the time course of wanted and unwanted effects with all doses is important. Constructing dose-response curves before the full effect is obtained shifts the curve to the right and reduces the apparent efficacy. We measured blood pressures after three months of treatment, when both blood pressure and

biochemical effects should have stabilised.⁸⁻¹⁰ If measurements had been taken earlier the antihypertensive effect of the 1.25 mg dose would not have been seen as it occurred slowly. The method of expressing the effect of antihypertensive drugs (in absolute figures, as a percentage reduction in blood pressure, or by number of responders) did not affect the conclusion.

Hypertensive patients who do not respond to thiazides are characterised by activation of the renin-angiotensin system and increased aldosterone concentrations.¹¹ Thus biochemical effects may differ between responders and non-responders. We found no such differences.

Increasing the dose of bendrofluazide increases the adverse biochemical effects but not hypertensive activity. Thiazides have been criticised mainly for their biochemical effects,^{12,13} but bendrofluazide at a dose of 1.25 mg caused only one relevant effect (a 6% increase in urate concentration). Thus much of the criticism of thiazides is based on use of too high doses.

Hypokalaemia induced by thiazides seems not to cause arrhythmias as was previously thought,^{14,15} but limiting hypokalaemia must be beneficial. A substudy of the Medical Research Council's trial found no benefit in potassium supplementation.¹⁶ Thus giving potassium with the bendrofluazide may not have been important. We found that the decrease in potassium concentration was mainly related to the dose of thiazide.

Thiazides are known to impair glucose tolerance.¹⁷ We found a clear correlation between the dose and an increase in fasting glucose concentrations, but only the 10 mg dose gave a significant effect. Recently the same effect was reported for hydrochlorothiazide at an average dose of 40 mg a day.¹⁸

Recently, interest has focused on adverse effects of hypertensive drugs on lipid profiles.^{19,20} Numerous studies have shown that diuretics adversely alter lipoprotein metabolism at least during short term trials, but this was found with high doses compared with the dose suggested by this study. It is unknown whether the effect on lipoprotein metabolism is related to dose.^{19,20} We showed clear relations between the dose of bendrofluazide and both total cholesterol and apolipoprotein B concentrations, which were consistent with the results of other studies.¹⁸⁻²⁰ We therefore conclude that the adverse effect of diuretics on lipoprotein metabolism is related to dose and could be avoided by prescribing lower doses. When evaluating comparative trials between thiazides and newer treatments it is important to be aware of the drug doses. A recent report claimed that captopril has less effect on glucose and lipoprotein metabolism than hydrochlorothiazide.¹⁸ The dose of hydrochlorothiazide was on average 40 (SD 12) mg, and thus more than 60% of the patients received an unrealistically high dose, creating a bias in favour of captopril.

Thiazides have been suggested to increase mortality and morbidity from acute myocardial infarction due to their effects on lipids.²¹ Re-evaluation of the data does not confirm this, and several trials have found that thiazides do not alter mortality and morbidity.^{2,22,23} The antihypertensive effect of thiazides may decrease the risk of acute myocardial infarction, but this is counteracted by increases in total and low density lipoprotein cholesterol concentrations. If the adverse lipid profile is considered important our findings suggest that new mortality studies using correct doses of thiazide should be performed.

The Medical Research Council's trial found an unexpectedly high number of subjective adverse effects.¹ Our study, although indicating that increasing the dose increases the number of adverse effects, was too small to be conclusive on this problem. A Medical Research Council substudy, which compared 5 and 10

mg bendrofluazide daily, found fewer adverse effects in the low dose group,¹⁶ as did a long term trial of the 5 mg dose.⁸ We found that the number of adverse effects in the group given 1.25 mg was the same as that in the group given placebo, although the effects were different. Patients' symptoms are known to change when they receive antihypertensive treatment. We conclude that in low doses thiazides are one of the most effective and well tolerated treatments for arterial hypertension.

- 1 Medical Research Council Working Party on Mild to Moderate Hypertension. Adverse reactions of bendrofluazide and propranolol for the treatment of mild hypertension. *Lancet* 1981;ii:539-43.
- 2 Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J* 1985;291:97-104.
- 3 1988 Joint National Committee. The 1988 report of the joint national committee on detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1988;148:1023-38.
- 4 Dunnett CW. Selection of the best treatment in comparison to a control with an application to a medical trial. In: Santner TJ, Tamhane AC, eds. *Design of experiments. Statistics: textbooks and monographs. Ranking and selection*. Vol 56. New York: Marcel Dekker, 1984: 47-66.
- 5 Gotzsche PC, Hvidberg EF, Juul P. Rational choice of dose: insufficient background knowledge? *Ration Drug Ther* 1986;20:1-7.
- 6 Ford RV, Nickell J. Experimental and laboratory reports: pharmacologic observations on a more potent benzothiadiazine diuretic (Be. 724-A). *Am Heart J* 1960;59:215-23.
- 7 Cranston WI, Juel-Jensen BE, Semmence AM, Jones RPCH, Forbes JA, Mutch LMM. Effects of oral diuretics on raised arterial pressure. *Lancet* 1963;ii:966-70.
- 8 Berglund G, Andersson O, Larsson O, Wilhelmsen L. Antihypertensive effect and side-effects of bendroflumethiazide and propranolol. *Acta Med Scand* 1976;199:499-506.
- 9 Papademetriou V, Price M, Johnson E, Smith M, Freis ED. Early changes in plasma and urine potassium in diuretic-treated patients with systemic hypertension. *Am J Cardiol* 1984;54:1015-9.

- 10 Wilkinson PR, Hesp R, Issler H, Raftery EB. Total body and serum potassium during prolonged thiazide therapy for essential hypertension. *Lancet* 1975;i:759-62.
- 11 Weber MA, Drayer JIM. Single-agent and combination therapy of essential hypertension. *Am Heart J* 1984;108:311-6.
- 12 McCarron DA. Diuretic therapy for mild hypertension: the "real" cost of treatment. *Am J Cardiol* 1984;53:9-11A.
- 13 Leren P, Foss OP, Helgeland A, Hjermann I, Holme I. Effects of pindolol and hydrochlorothiazide on blood lipids—the Oslo study. *Clinical Trials Journal* 1981;18:254-61.
- 14 Medical Research Council Working Party on Mild to Moderate Hypertension. Ventricular extrasystoles during thiazide treatment: substudy of MRC mild hypertension trial. *Br Med J* 1983;287:1249-53.
- 15 Papademetriou V, Burris JF, Notargiacomo A, Fletcher RD, Freis ED. Thiazide therapy is not a cause of arrhythmia in patients with systemic hypertension. *Arch Intern Med* 1988;148:1272-6.
- 16 Medical Research Council Working Party. Comparison of the antihypertensive efficacy and adverse reactions to two doses of bendrofluazide and hydrochlorothiazide and the effect of potassium supplementation on the hypotensive action of bendrofluazide: substudies of the Medical Research Council's trials of treatment of mild hypertension. *J Clin Pharmacol* 1987;27:271-7.
- 17 Veterans Administration Cooperative Study Group on Antihypertensive Agents. Propranolol or hydrochlorothiazide alone for the initial treatment of hypertension. *Hypertension* 1985;7:1008-16.
- 18 Pollare T, Lithell H, Berne C. A comparison of the effect of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 1989;321:868-73.
- 19 Ames RP. Antihypertensive drugs and lipid profiles. *Am J Hypertens* 1988;1:421-7.
- 20 Lardinois CK, Neuman SL. The effects of antihypertensive agents on serum lipids and lipoproteins. *Arch Intern Med* 1988;148:1280-8.
- 21 Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results. *JAMA* 1982;248:1465-7.
- 22 Management Committee. The Australian therapeutic trial in mild hypertension. *Lancet* 1980;ii:1261-7.
- 23 Wilhelmsen L, Berglund G, Elmfeldt D, et al. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J Hypertens* 1987;5:561-72.

(Accepted 7 February 1990)

Managing seizures in the casualty department

Paul J W McKee, Elaine A Wilson,
Jean A Dawson, John G Larkin, Martin J Brodie

Epilepsy has a prevalence of 1 in 200¹: roughly 5% of the population can expect to have a seizure at some time.² Anyone experiencing a first fit is likely to be referred as an emergency. There have been studies in the United States of how such patients are managed,³ but none have been reported from the United Kingdom. We report on the management of patients who presented over two years at a casualty department after a seizure.

Patients, methods, and results

We obtained the names of patients recorded as having had a "seizure" or a "blackout" in 1985 and 1986 from the casualty register of this hospital, a 600 bed teaching hospital serving a population of 325 000. One or more of the following criteria were required: (a) description by an independent witness; (b) appropriate history with postictal clinical signs; (c) a further witnessed seizure in the casualty department; (d) loss of consciousness in a patient known to have epilepsy. We obtained the hospital case sheet for each patient and completed a standard form from the data available during the year after the initial presentation.

From a total of 50 000 referrals in 1985 and 1986 we identified seizures in 597 patients (370 (62%) men, 227 (38%) women; mean age 41 years, range 12-88 years). Of these, 260 (44%) patients (mean age 44) had had their first fit. The other 337 patients (mean age 38) were known to have epilepsy, and the presenting event was regarded as a "recurrent" seizure.

Of the seizures, 498 (83.5%) were generalised tonic-clonic fits. Sixty seven (11.3%) of the patients pre-

Possible predisposing factors in 317 patients presenting to an emergency department after a seizure

	First seizure (n=155)	Recurrent seizure (n=162)	Total (%) (n=317)
Alcohol abuse	96	97	193 (60)
Head injury	17	31	48 (15)
Vascular accident	13	9	22 (7)
Neoplasm	8	5	13 (4)
Infection	1	9	10 (3)
Atrophy	8	2	10 (3)
Drug related	7	2	9 (3)
Metabolic abnormality	5	3	8 (3)
Arteriovenous malformation	0	4	4 (2)

sented with a complex partial seizure, and 15 (2.5%) had multiple episodes. Only 11 patients were admitted in status epilepticus. One reported a simple partial seizure, and a further four fits remained unclassified. The table lists possible predisposing factors in 317 (53%) patients.

After referral 331 (55%) patients were being treated with one or more anticonvulsant drugs (20% who had a first seizure, 80% who had recurrent seizures). Of these, 251 (76%) took one drug (carbamazepine 93, phenytoin 83, sodium valproate 45, phenobarbitone 23, primidone 7), 70 (21%) took two drugs, and 10 (3%) took three drugs. More patients with an "abnormal" electroencephalogram received anticonvulsant drugs (n=303, 62% abnormal v 39% normal, χ^2 test: $p<0.005$). This was not the case with positive results of computed tomography (n=106, 62% abnormal v 60% normal).

Of the 260 patients with a first seizure, 46 (18%) were discharged immediately and 28 given a follow up appointment. The other 214 patients were admitted to hospital: 137 (64%) spent under 48 hours in a short stay facility, and 46 (18%) were investigated in a general medical ward. Overall, of the 597 patients 371 (62%) (167 with a first seizure; 204 with recurrent seizures) subsequently attended an outpatient clinic. Most (208; 56%) were seen by a general physician (127 (76%) first seizure, 79 (39%) recurrent seizure); 93 (36%) patients with a first seizure and 133 (40%) with recurrent seizures did not attend for follow up.

Epilepsy Research Unit,
University Department of
Medicine and
Therapeutics, Western
Infirmary, Glasgow
G11 6NT

Paul J W McKee, MRCP,
medical registrar
Elaine A Wilson, MB, junior
house officer
Jean A Dawson, deputy
medical records officer
John G Larkin, MRCP,
research fellow
Martin J Brodie, FRCP,
consultant clinical
pharmacologist

Correspondence to:
Dr Brodie.

Br Med J 1990;300:978-9