PAPERS AND SHORT REPORTS

Pilot study of combination treatment for gall stones with medium dose chenodeoxycholic acid and a terpene preparation

W R ELLIS, K W SOMERVILLE, B H WHITTEN, G D BELL

Abstract

Thirty patients with radiolucent stones in a radiologically functioning gall bladder were treated for up to two years with a combination of Rowachol (one capsule twice daily), a mixture of cyclic monoterpenes, and chenodeoxycholic acid (7·0-10·5 mg/kg/day). The patients were not selected for body weight or size of stones. All complete dissolutions diagnosed by oral cholecystography were confirmed or refuted by ultrasound examination. Control of symptoms was excellent, only one patient withdrawing from the study because of persistent biliary pain. No evidence of hepatotoxicity was detected biochemically, and diarrhoea due to chenodeoxycholic acid was minimal at this dose. Stones disappeared completely in 11 patients (37%) within one year and in 15 (50%) within two years. These results compared favourably with those obtained with similar doses of chenodeoxycholic acid alone, in particular those of the National Co-operative Gallstone Study (complete dissolution in 13·5% of patients at two years).

Treatment with a combination of medium dose chenodeoxycholic acid with Rowachol for radiolucent gall stones is economical, effective, and likely to minimise persistent symptoms and adverse effects of treatment.

Introduction

Drugs taken by mouth to dissolve gall stones have been an established therapeutic option since the initial reports of the use of chenodeoxycholic acid for this purpose appeared in 1972.[1 2] Since then ursodeoxycholic acid has also been widely used, and many reports have accumulated on the efficacy, safety, applicability, and possible mechanisms of action of treatment with bile acids. The clinical position has recently been reviewed[3 4]; confusion, however, remains, particularly regarding efficacy, as many earlier studies were uncontrolled and used widely differing doses and periods of treatment. In this context the recent publication of the results of the National Co-operative Gallstone Study made a valuable contribution.[5] Although criticised on the grounds of inadequate dosage of chenodeoxycholic acid,[6] the study was a controlled investigation in a large series of patients who were selected only for the presence of radiolucent stones in a functioning gall bladder. As such, the study must now be the yardstick against which alternative regimens, including our own combinations of chenodeoxycholic acid with Rowachol (Rowa, Bantry, Ireland), are assessed.

Rowachol is an inexpensive preparation of six cyclic monoterpenes in olive oil and has choleretic[7] and spasmolytic[8] properties. Radiographically documented dissolution of gall stones during treatment with Rowachol has been described often,[9-16] but its efficacy is inferior to that of full dose bile acids. In a previous study, however, by combining Rowachol with low dose (375 mg daily) chenodeoxycholic acid we achieved complete dissolutions within one year in six out of 22 (27%) patients not selected for body weight or stone size. This compared well with results of treatment with full dose bile acids in similar patients and resulted in financial savings and improved tolerance by patients of treatment.[17] We suspected a genuinely synergistic action of the terpenes, for which we suggested several possible mechanisms.[18] Further support for this contention came from the National Co-operative Gallstone Study, in which response to the same dose of chenodeoxycholic acid alone was poor (complete dissolution in 16 out of 306 patients (5%) after two years' treatment).[5]

We now report an open pilot study in which patients were treated with a combination of Rowachol and chenodeoxycholic acid. Chenodeoxycholic acid was given in a dose of 7·0-10·5 mg/kg/day, which was still below the optimum but only a little lower on average than the 750 mg/day used in the National

Department of Therapeutics, City Hospital, Nottingham NG5 1PB
W R ELLIS, MRCP, research fellow and honorary senior registrar
K W SOMERVILLE, FRACP, lecturer and honorary senior registrar
B H WHITTEN, MD, research fellow
G D BELL, MD, FRCP, senior lecturer and honorary consultant physician

Correspondence to: Dr W R Ellis, Department of Medicine, St James's University Hospital, Leeds LS9 7TF.

Co-operative Gallstone Study. This intermediate dose was chosen to achieve competitive therapeutic results without undue increases in side effects or costs. The open design was adopted to permit the rapid accumulation of enough treated patients to indicate the likely efficacy and acceptability of the combination before planning more rigorous large scale studies.

Patients and methods

Thirty patients (table I), presenting between February 1979 and July 1982 at an open access clinic for cases of known gall stone disease, were treated for two years or until earlier dissolution of gall stones or withdrawal. Treatment was offered to all patients with radiolucent stones in a radiologically functioning gall bladder; patients were not selected for body weight or size of gall stones. Assessment of symptoms and biochemical monitoring were undertaken every six weeks. Oral cholecystography was performed before entry to the study and at intervals of six months: complete dissolution was not diagnosed unless ultrasound examination of the gall bladder also yielded negative results for stones.[19]

TABLE I—*Details of patients treated*

Case No	Sex	Age (years)	Weight (kg)	Diameter of largest stone (cm)	Dose of chenodeoxycholic acid (mg (mg/kg))
1	F	32	67·1	0·5	500 (7·5)
2	F	26	52·0	0·7	500 (9·6)
3	F	74	68·0	1·2	625 (9·2)
4	M	61	65·0	1·1	500 (7·7)
5	M	74	85·3	1·0	750 (9·4)
6	M	64	95·2*	0·5	875 (9·2)
7	F	62	105·0*	0·7	750 (7·1)
8	F	55	71·0	1·0	625 (8·8)
9	F	29	96·6*	1·0	875 (8·9)
10	F	39	76·7	0·5	625 (9·5)
11	F	36	76·5	0·5	500 (8·0)
12	F	50	62·1	0·7	625 (10·1)
13	F	65	58·5	1·5	500 (8·6)
14	F	72	64·9	0·7	500 (7·7)
15	F	31	81·6*	2·0†	625 (7·7)
16	F	32	47·7	0·3	500 (10·5)
17	F	35	94·8*	0·5	875 (9·2)
18	F	68	53·5	0·5	500 (9·4)
19	F	58	73·5	1·3	750 (10·2)
20	F	47	63·5	1·7†	500 (7·9)
21	M	66	90·4*	1·6†	750 (8·3)
22	F	48	79·4	0·7	625 (9·9)
23	F	69	60·8	0·5	625 (10·3)
24	F	73	73·5	1·5	625 (8·5)
25	F	76	68·5	1·5	500 (7·5)
26	F	59	60·3	1·8†	500 (8·3)
27	F	57	86·6	1·6†	750 (8·7)
28	M	67	90·3	2·0†	750 (8·3)
29	F	44	75·8	0·8	625 (8·3)
30	F	59	68·2	1·2	625 (9·2)
Mean (SEM)		54·3 (2·9)	73·3 (2·7)	1·04 (0·09)	629·2 (8·8 (22·8) (0·2))
Mean (SEM) for women		51·8 (3·2)	70·9 (2·8)	1·00 (0·10)	610·0 (8·8 (22·7) (0·2))
Mean (SEM) for men		66·4 (2·2)	85·2 (5·3)	1·24 (0·23)	725 (8·6 (54·8) (0·3))

*Patient more than 130% ideal body weight.
†Stones larger than 1·5 cm in diameter.

Results

Treatment was generally well tolerated; only one patient noted appreciable diarrhoea, which was not sufficient to necessitate reduction in dosage. All patients remained within the study for the first six months, after which four were removed. Two of these four underwent surgery, one because her stones had enlarged during treatment and the other because he finally accepted that his stones were unlikely to dissolve (because of obesity and failure to reduce weight) and because he was having two or three attacks of biliary colic a year, the most recent of which had necessitated admission to hospital. The third patient to withdraw had ursodeoxycholic acid added to his regimen, and the fourth was an elderly diabetic woman who sustained a cerebral infarction. A further patient had an attack of cholecystitis at six months, which was successfully treated with antibiotics and glucagon infusion. She opted to continue treatment, and her stones had dissolved after a further six months.

After a year four more patients left the study and underwent surgery, one because of persistent non-function of the gall bladder, the three others as a result of advice given about the prognosis for dissolution on the grounds of the size of the stone, body weight, or progress so far, or a combination of these. Persistent symptoms had not been a problem in any of these four patients. At 18 months two patients were withdrawn and their treatment changed. One had abdominal discomfort of irritable bowel type, of which he had complained before starting treatment; he refused to continue with the regimen, even though his stones were showing progressive dissolution.

Only one patient received the treatment for two years without showing at least partial dissolution. She and a patient showing partial dissolution continued treatment beyond two years. Two further patients yielded negative results to cholecystography but positive results to ultrasound examinations after two years and continued treatment. At the end of the study one patient had only had treatment for a year but already showed partial dissolution. Complete dissolution occurred in 15 (50%) of our patients; in 11 (37%) it occurred within one year of starting treatment (figure).

Table II shows the results of liver function tests in our patients. All individual changes were temporally related to attacks of colic or cholecystitis.

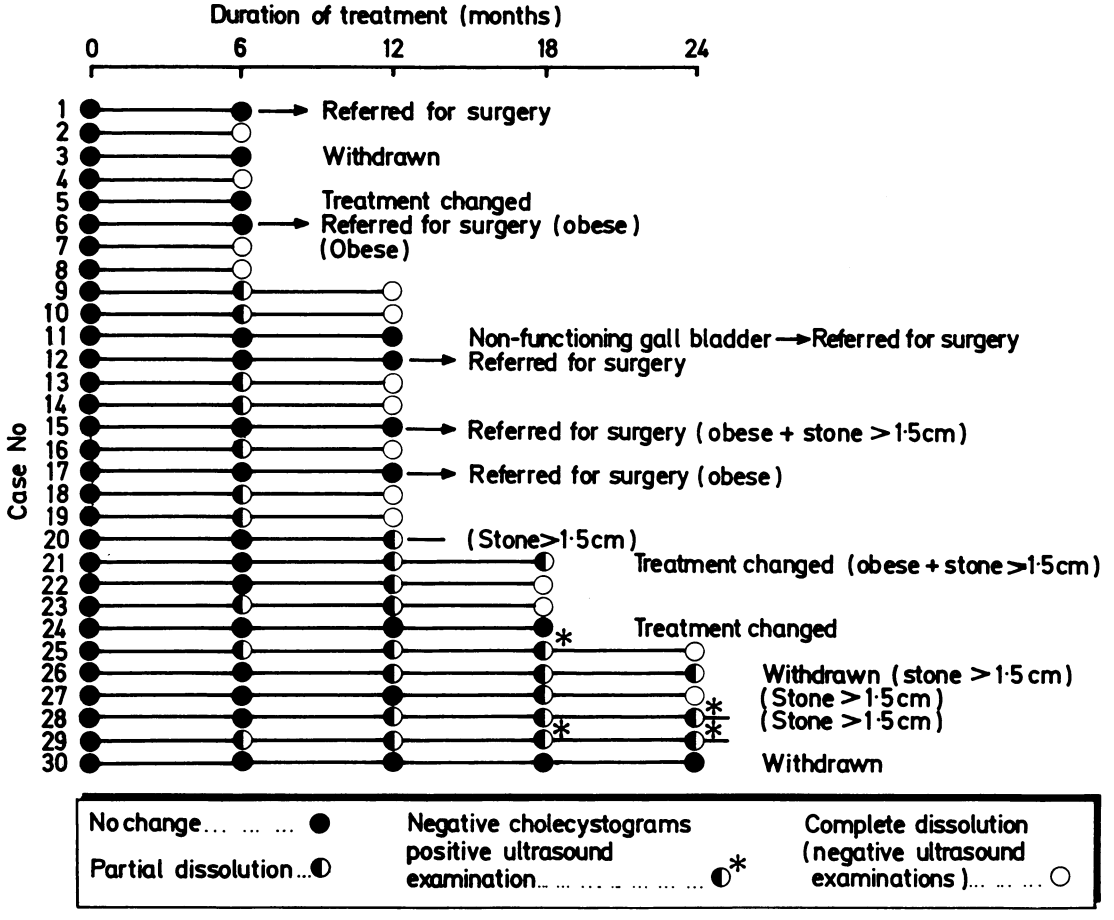
TABLE II—*Mean (SD) results of liver function tests in 30 patients with gall stones treated with Rowachol (two capsules daily) and chenodeoxycholic acid (mean 629 mg/day)*

	Reference range	Before treatment (n = 30)	After 3 months' treatment (n = 28)	After 6 months' treatment (n = 28)	After 9 months' treatment (n = 20)	After 12 months' treatment (n = 20)
Alkaline phosphatase (IU/l)	46-190	119 (44)	131 (77)	113 (42)	109 (32)	107 (38)
Serum alanine transaminase (IU/l)	2-21	14 (7)	16 (10)	15 (9)	13 (5)	13 (6)
Bilirubin (μmol/l)	5-17	11 (5)	11 (4)	11 (5)	9 (5)	11 (6)
γ-Glutamyltransferase (IU/l)	6-28	19 (21)	19 (21)	17 (21)	16 (14)	17 (18)*

*n = 19.
Conversion: SI to traditional units—Bilirubin: 1 μmol/l ≈ 58·47 μg/100 ml.

Discussion

Although this was not a controlled study, it showed an encouraging response to treatment with a combination of Rowachol and below optimal doses of chenodeoxycholic acid in patients who were not selected in any way for features associated with good results of treatment. The importance of size of stone and body weight in determining response to treatment with bile acid is well recognised.[20] Table I shows that six patients had stones over 1·5 cm in diameter and six patients were more than 130% of ideal weight for height.[21] Stones dissolved in two obese patients (cases 7 and 9) receiving mean doses of chenodeoxycholic acid of less than 10 mg/kg/day in combination with Rowachol; such patients usually require 18-20 mg/kg/day to achieve desaturation of bile with chenodeoxycholic acid alone.[22] If obese patients are excluded from the series, only 24 patients remain, in nine of whom (38%) stones dissolved completely within one year and in 13 (54%) within two years. Excluding patients with large (>1·5 cm) stones, there were 24 patients, in 11 of whom (46%) stones dissolved completely within one year and in 14 (58%) within two years. Exclusion of both groups leaves a total of 20 patients, in nine of whom (45%) stones dissolved completely within one year and in 12 (60%) within two years. These adjusted rates of dissolution are not substantially different from the response in the group as a whole; although the numbers are small, the response of the group as a whole suggests that when Rowachol



Result in 30 patients with radiolucent gall stones of treatment with Rowachol (two capsules daily) and chenodeoxycholic acid (mean (SEM) dose 629·2 (22·8) mg/day).

is used the criteria for selecting patients for treatment need not be as stringent. One of us (WRE) had previously suspected that obese subjects may respond as well as, or better than, non-obese subjects to treatment with terpenes alone (Gallstone dissolution using terpenes. Thesis submitted to University of Nottingham, 1983); this may be related to the curious dose response of the biliary lipids to Rowachol, in which excessive doses produce an increase in cholesterol saturation (WRE. Thesis submitted 1983).[23] On this basis, we would recommend that the dose used in the present series, two capsules daily, is not exceeded.

This is the first report of a series in which all complete dissolutions of stones were confirmed by ultrasonography as well as by oral cholecystography. Our experience has indicated that diagnosis of dissolution by oral cholecystography alone will often be erroneous because small fragments that are below the limits of resolution of the technique but detectable by ultrasound examination may persist.[19] This has also been seen by others[24] and suggests that previously reported incidences of dissolution may have been spuriously high. In the present series complete dissolution could have been diagnosed in two further patients on the criteria of oral cholecystography alone and the overall incidence of dissolution would thus have been 17 out of 30 (57%) at two years.

Comparison of our results with those of the National Co-operative Gallstone Study, which used chenodeoxycholic acid alone and in which ultrasound was not used, is, however, favourable. Although the two series were from different countries, the groups were similar in terms of age and weight (table III) and in that neither was selected to exclude large stones or obese subjects. Furthermore, other published reports suggest that the results of treatment with 750 mg daily of chenodeoxycholic acid in similarly unselected patients in the United Kingdom[25] and other Western type populations[26 27] are comparable with those of the National Co-operative Gallstone Study.[5] The occurrence in our series of complete dissolutions in 15 (50%) of our patients within two years compared with 13·5% in the National Co-operative Gallstone Study[5] is therefore striking. Although our patients may have derived some advantage from taking their chenodeoxycholic acid in a single night time dose,[28] which was tailored to body weight,[29 30] there are doubts about the absorption and bioavailability of large doses of chenodeoxycholic acid,[31] and not everybody finds that doses related to weight are preferable to fixed ones.[25] Thus our results suggest a useful adjuvant role for Rowachol. This would be best confirmed by a formal double blind study. Such a study is currently in progress in other centres, using ursodeoxycholic acid in full dosage with and without Rowachol.

At the dose of chenodeoxycholic acid used, diarrhoea was not a problem[26] and patient tolerance was excellent. There was no evidence of drug toxicity, and control of symptoms was satisfactory, only one patient having to be referred for surgery because of continuing biliary pain. We therefore consider that a combination of Rowachol with medium dose (7·0-10·5 mg/kg/day) treatment with chenodeoxycholic acid is a safe and

TABLE III—*Comparison of mean (SEM) findings for patients in the present series with those for patients in the National Co-operative Gallstone Study who received high doses (750 mg/day) of chenodeoxycholic acid*

	Patients in the National Co-operative Gallstone study	This series
Mean age of men (years)	52·9 (0·9)	66·4 (2·2)
Mean age of women (years)	56·8 (0·8)	51·8 (3·2)
Mean weight of men (kg)	82·9 (1·2)	85·2 (5·3)
Mean weight of women (kg)	70·6 (1·2)	70·9 (2·8)
Mean dose of chenodeoxycholic acid:		
For all patients (mg)	All 750	629 (22·8)
For men (mg/kg)	9·1	8·6 (0·3)
For women (mg/kg)	10·6	8·8 (0·2)

acceptable alternative to full dose treatment with bile acid for radiolucent gall stones, which is likely to offer added benefits in the shape of good control of symptoms and reduced costs.

We thank Rowa Ltd for supplies of Rowachol capsules and financial support of WRE during a research fellowship. We also thank Dr D H Rose and Dr D R Knapp for the ultrasound examinations and cholecystogram reports.

References

1 Danzinger RG, Hofmann AF, Schoenfield LJ, *et al.* Dissolution of cholesterol gallstones by chenodeoxycholic acid. *N Engl J Med* 1972;**286**:1-8.
2 Bell GD, Whitney B, Dowling RH. Gallstone dissolution in man using chenodeoxycholic acid. *Lancet* 1972;ii:1213-6.
3 Iser JH, Sali A. Chenodeoxycholic acid: a review of its pharmacological properties and therapeutic use. *Drugs* 1981;**21**:90-114.
4 Bachrach WH, Hofmann AF. Ursodeoxycholic acid in the treatment of cholesterol cholelithiasis. *Dig Dis Sci* 1982;**27**:737-61 and 833-56.
5 Schoenfield LJ, Lachin JM. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: the National Co-operative Gallstone Study. *Ann Intern Med* 1981; **95**:257-82.
6 Anonymous. Dissolving hopes for gallstone dissolution? *Lancet* 1981;ii:905-6.
7 Mörsdorf K. Les terpènes cycliques et leur action choléretique. *Bulletin de Chimie Therapeutique* 1965;**4**:442-443.
8 Boettge K. Atherische Ole und Spasmolyse. *Medizinische Monatsschrift* 1954;**8**: 444-6.
9 Offergeld H. *Basis of the therapy of the cholecystopathies. 55th medical congress, Berlin.* Bantry: Rowa, 1952. Available on request from Rowa Ltd.
10 Sarreither W. Rowachol, ein terpenhaltiges Praparat zur Behandlung der Cholelithiasis. *Medizinische Monattsschrift* 1955;**9**:97-9.
11 Greif S. *Empirical report on Rowachol.* Bantry: Rowa, 1956. Available on request from Rowa Ltd.
12 Okabe H. Clinical experience with terpene preparation (Rowachol) in treatment of disease of the gallbladder and cystic duct. *Shokakibyo No Rinsho* 1960;**12**: 12-7.
13 Kameda H. Clinical investigations of disease of the gallbladder and the biliary tract, in particular the results of infra-red spectrophotometric examination. *Naika Hokan* 1960;**6**:3-15.
14 Noda H, Kuriyama S, Tokuda A. Clinicopathological studies on cholelithiasis. II. Medical treatment of cholelithiasis—experience with terebene oil preparation. *Naika Hokan* 1965;**12**:505-11.
15 Hordinsky BZ. Terpenes in the treatment of gallstones. *Minn Med* 1971;**54**:649-52.
16 Bell GD, Doran J. Gall stone dissolution in man using an essential oil preparation. *Br Med J* 1979;i:24.
17 Ellis WR, Middleton B, White DA, *et al.* Adjunct to bile acid treatment for gallstone dissolution: low-dose chenodeoxycholic acid combined with a terpene preparation. *Br Med J* 1981;**282**:611-2.
18 Bell GD, Clegg RJ, Ellis WR, *et al.* How does Rowachol, a mixture of plant monoterpenes, enhance the cholelitholytic potential of low and medium dose chenodeoxycholic acid? *Br J Pharmacol* 1982;**13**:278-9.
19 Somerville KW, Rose DH, Bell GD, *et al.* Gallstone dissolution and recurrence: are we being misled? *Br Med J* 1982;**284**:1295-7.
20 Dowling RH. Medical treatment of gallstones with CDCA and UDCA. In: Paumgartner G, Stiehl A, Gerok W, eds. *Bile acids and lipids.* Lancaster: MTP Press, 1981:329-39.
21 Metropolitan Life Insurance Company. *Statistical bulletin.* New York: Metropolitan Life Insurance Co, 1959.
22 Iser JH, Maton PN, Murphy GM, *et al.* Resistance to chenodeoxycholic acid (CDCA) treatment in obese patients with gallstones. *Br Med J* 1978;i:1509-12.
23 Doran J, Keighley MRB, Bell GD. Rowachol—a possible treatment for cholesterol gallstones. *Gut* 1979;**20**:312-7.
24 Shapero TF, Rosen IE, Wilson SR, *et al.* Discrepancy between ultrasound and oral cholecystography in the assessment of gallstone dissolution. *Hepatology* 1982;**2**:587-90.
25 Bateson MC, Ross PE, Murison J, *et al.* Comparison of fixed doses of chenodeoxycholic acid for gallstone dissolution. *Lancet* 1978;i:1111-4.
26 Gerolami A, Sarles H. Brette R, *et al.* Controlled trial of chenodeoxycholic acid therapy for radiolucent gallstones. *Digestion* 1977;**16**:299-307.
27 Toouli J, Jablonski P, Watts JMcK. Treatment of gallstones by chenodeoxycholic acid. *Med J Aust* 1980;**1**:478-9.
28 Maudgal DP, Bird R, Northfield TC. Optimal timing of doses of chenic acid in patients with gallstones. *Br Med J* 1979;i:922-3.
29 Mok HYI, Bell GD, Dowling RH. Effect of different doses of chenodeoxycholic acid on bile lipid composition and on frequency of side effects in patients with gallstones. *Lancet* 1974;ii:253-7.
30 Thistle JL, Hofmann AF, Yu PYS, *et al.* Effect of varying doses of chenodeoxycholic acid on bile lipid and biliary bile acid composition in gallstone patients: a dose-response study. *American Journal of Digestive Diseases* 1972;**22**:1-6.
31 Ponz de Leon M, Loria P, Carulli N, *et al.* Intestinal solubilization, absorption, pharmacokinetics and bioavailability of chenodeoxycholic acid. *Eur J Clin Invest* 1980;**10**:261-71.

(Accepted 4 May 1984)

Effects of treatment for hypertension on cerebral haemorrhage and infarction

D G BLACK, A M HEAGERTY, R F BING, H THURSTON, J D SWALES

Abstract

One hundred and sixty nine patients admitted to hospital for stroke over 30 months were examined to see whether treating hypertension had influenced the incidence of cerebral haemorrhage and infarction. Seventy eight (46%) of them had normal blood pressure, 47 (28%) previously diagnosed hypertension for which they were receiving treatment, and 44 (26%) previously undiagnosed and untreated hypertension. Haemorrhagic stroke was commoner among patients with untreated hypertension, whereas infarction was commoner in patients with treated hypertension. Infarction and haemorrhage were equally prevalent in patients with normal blood pressure.

Effective treatment in this population seemed to have had a substantially different impact on vascular disease, giving rise to cerebral haemorrhage as opposed to infarction. This is consistent with evidence from other studies that treatment for hypertension has little or no effect on the progression of atheroma.

City Hospital, Nottingham
D G BLACK, MB, senior house officer in medicine

Department of Medicine, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX
A M HEAGERTY, MB, MRCP, lecturer in medicine
R F BING, MB, MRCP, senior lecturer in medicine
H THURSTON, MD, FRCP, reader in medicine
J D SWALES, MD, FRCP, professor of medicine

Correspondence to: Dr A M Heagerty.

Introduction

Hypertension is the most important known cause of strokes in men and women of all ages.[1] Despite a fall in the incidence of fatal strokes in some countries[2] cerebrovascular disease still remains a major cause of death and disability, particularly among elderly people, though effective control of blood pressure has been confirmed to reduce the incidence of stroke in patients with moderate or severe hypertension[3] and produce a dramatic improvement in prognosis among patients at highest risk.[4]

Theoretically there could be two explanations for the continuing high incidence of strokes despite widespread availability of effective antihypertensive drugs. Strokes might be the result of untreated hypertension, or, alternatively, of hypertension for which treatment is, at least when started, partially or wholly ineffective. Epidemiological evidence suggests that hypertension remains an important treatable cause of death in the United Kingdom,[5] and there can be little doubt that even patients at high risk go untreated. On the other hand, not all vascular pathological abnormalities associated with hypertension are reversed by control of blood pressure. Thus in most studies treatment for hypertension has had a disappointingly small effect on incidence of myocardial infarction.[3 6] Strokes in patients