Using a different regimen of 200-mg oral atenolol at 12-hour intervals I have observed a similar fall in blood pressure over 24 hours, with some fluctuation. The pulse rate remained below 60 beats a minute after four hours. Hence increasing the dose of atenolol will probably not achieve better blood pressure control. In any case, in severe hypertension with grade 3 or 4 retinopathy it is probably unnecessary to bring the blood pressure down faster. However, labetalol acts more quickly and the blood pressure may be normalised within two or four hours after oral administration[1] with either a 200-mg, 300-mg, or 400-mg starting dose. Sometimes blood pressure is not normalised even with a 400-mg dose, and a 400-mg eight hourly regimen is required. The 400-mg starting dose has not been associated with significant hypotension. Presumably the prompt and potent effect of labetalol in severe hypertension is due to a combination of β- and α-receptor blockade. In addition, beta-blockade stabilises heart rate. Various vasodilators such as minoxidil[2] and captopril[3] have been used for hypertensive emergencies, and chlorpromazine and frusemide are also effective.[4] In severe hypertensive heart failure prazosin, in a standard starting dose of 0·5 mg eight hourly, combined with intravenous frusemide or bumetanide successfully unloads the heart as well as controlling blood pressure.

Titrating oral antihypertensive drugs against blood pressure is unpredictable and inflexible; but it may be justified on the practical grounds of simplicity of administration, overall effectiveness, and relative lack of complications.

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[1] Ghose RR. *Br J Clin Pharmacol* 1979;**8**, suppl:189-93.
[2] Bauer JH, Alpert NA. *Journal of Cardiovascular Pharmacology* 1980; suppl II:189-99.
[3] Case DB, Atlas SA, Sullivan P, Laragh JH. *Circulation* 1979;**59-60**, suppl II:130 (abstract).
[4] Young RJ, Lawson AAH, Malone DNS. *Br Med J* 1980;**289**:1579.

SIR,—As Drs L T Bannan and D G Beevers indicate (30 May, p 1757), even oral antihypertensive therapy for swift reduction in blood pressure may cause cerebral or retinal ischaemia. Though they found a single 100-mg dose of oral atenolol to achieve satisfactory blood pressure reduction without such complications in 10 hypertensive subjects, we have recently observed a patient whose response to the same dose of oral atenolol suggests that this may not always be the case with this drug.

The patient was a 50-year-old Indian with an eight-year history of hypertension due to renal artery stenosis. Blood pressure control had been poor despite a variety of antihypertensive drugs: diuretics, beta-blockers (including atenolol at a maximum dose of 200 mg daily), vasodilators, methyldopa, and captopril. An iliorenal saphenous vein graft in January 1980 had also failed to control the blood pressure. On admission in December 1980 he showed evidence of left ventricular hypertrophy, but the fundi were normal and there was no haematuria, and only minimal proteinuria. Creatinine clearance was 44 ml/minute. Blood pressure averaged 170/110 mm Hg on frusemide 80 mg daily only. It was felt that drug compliance at home was poor.

In February 1981 in outpatients the blood pressure was 240/140 mm Hg. The fundi were normal and the patient had no symptoms. Atenolol 100 mg daily was prescribed. Next day he was admitted having developed first lassitude and dizziness and then headache and weakness some four hours after taking the first tablet of atenolol. He denied chest or back pain. On examination blood pressure was 135/80 mm Hg and pulse 48 beats/min. He had a rapidly improving left hemiparesis. The fundi were normal, and all major pulses—in particular, the carotid arteries—were normal. No bruits were heard. There was no change in the electrocardiogram, which showed a sinus bradycardia. An episode of cerebral ischaemia secondary to acute hypotension was diagnosed, and it was felt that recovery from the effect of the drug was now taking place. However, his weakness returned a few hours later despite no further fall in the blood pressure. A complete hemiplegia developed; he became unconscious and died some hours later. Permission for postmortem examination was not obtained.

It seems likely that this patient died from cerebral infarction due to acute hypotension caused by sudden, severe beta-blockade. The timing would implicate atenolol, but why he became so sensitive to a drug which he had taken previously in higher dosage without ill effect is not explained. It is of interest that the hypertension had not entered a malignant phase and therefore autoregulation of cerebral blood flow might have been expected to operate successfully at the systolic pressures observed, with preservation of cerebral perfusion. Other causes of decreased cerebral perfusion, particularly major vessel stenosis, were not evident clinically, but could not be totally excluded without a postmortem examination.

Recently emphasis has been placed on cautious, preferably oral, treatment of severe hypertension.[1] Our case serves to emphasise that with today's powerful drugs it may not be possible to avoid lowering the blood pressure too much on every occasion.

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Influence of cimetidine on pharmacokinetics of propranolol

SIR,—We read with interest the recent paper by Dr A M Haegerty and others on the influence of cimetidine on the pharmacokinetics of propranolol (13 June, p 1917). In the discussion the authors list a number of conditions that are known to affect the pharmacokinetics of propranolol. These were smoking, liver disease, chronic renal failure, and thyroid disease; and all were excluded in this study. No mention was made, however, of inflammatory diseases that have been shown by us to raise plasma propranolol concentrations dramatically.[1]

The exclusion of patients with any type of inflammatory disease as indicated by a raised erythrocyte sedimentation rate is of importance if the results are to be meaningful, as even minor illnesses may affect the plasma concentrations of some β-adrenoceptor blocking agents.[2]

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[1] Schneider RE, Bishop H, Hawkins CF. *Br J Clin Pharmacol* 1979;**8**:43-7.
[2] Kendall MJ, Quarterman CP, Bishop H, Schneider RE. *Br Med J* 1979;ii:465-8.

Dangers of amiodarone and anticoagulant treatment

SIR,—We read with interest the recent reports describing an interaction between amiodarone and warfarin by Dr A Rees and his colleagues (30 May, p 1756) and Martinowitz *et al*[1] and have recently had an opportunity to investigate the mechanism of this interaction.

A 65-year-old man was admitted to hospital with an anterolateral myocardial infarct. Twelve days later he had a cardiac arrest in ventricular fibrillation, from which he was successfully resuscitated. Despite therapy with lignocaine, mexiletine, and procainamide he continued to have episodes of ventricular tachycardia; and therefore on day 19 treatment was commenced with amiodarone (300 mg intravenously followed by 200 mg four times a day by mouth). He had been given anticoagulant treatment on admission and since day 6 had received warfarin 4 mg daily, which had maintained his prothrombin time within the therapeutic range (24-36 seconds). On the third and fourth days after starting amiodarone (days 22 and 23 after infarction) his prothrombin time increased to 42 and 94 seconds respectively despite the fact that warfarin was stopped on day 22. Unfortunately on day 24 he had a further cardiac arrest, from which he could not be resuscitated. Subsequent measurement of plasma warfarin concentrations (by gas-liquid chromatography) showed a marked rise in concentration from 1·56 μmol/l before he started on amiodarone (day 19) to 3·04 μmol/l after four days' amiodarone treatment (table). Plasma protein binding of warfarin (measured by equilibrium dialysis) did not alter.

Effect of amiodarone on plasma warfarin concentration and prothrombin time (PT)

Days after starting amiodarone	Plasma warfarin (μmol/l) concentration	% Unbound warfarin	PT (s)
Before amiodarone	1·56	2·26	34
Day 1	1·77	2·16	34
Day 2	2·05	2·25	28
Day 3	2·82	—	42
Day 4	3·04	2·15	94

While haemodynamic factors cannot be excluded as one cause for the change in prothrombin time, the rise in plasma warfarin concentration following the addition of amiodarone suggests that the mechanism of this interaction is probably inhibition of warfarin metabolism.

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Cardiovascular disease and hormone replacement treatment

SIR,—Dr Sheila Adams and others (18 April, p 1277) confirm the absence of an association between oestrogen use and fatal myocardial infarction or subarachnoid haemorrhage in older women. While gratified to find our earlier reports[1-3] confirmed, we are concerned that there is a very serious risk of a type II error.

Current users are very few among women with acute myocardial infarction and their controls—two and five respectively—and