Thiazide Withdrawal in Hypertension

R. M. BOYLE, MB, MRCP(UK), M. L. PRICE, BM, MRCP(UK) and M. HAMILTON, MD, FRCP
Chelmsford and Essex Hospital

Introduction

In 1956, McCubbin et al. demonstrated the upward resetting of baroreceptors in dogs subjected to renovascular hypertension. Subsequently, Page and Dustom (1962) postulated that long-term reduction of blood pressure may reset the baroreceptors in a downward direction and so obviate the need for continuous therapy.

Previous studies on the effect of withdrawing treatment in hypertension produced variable results. Page and Dustom (1962) reported that 9 (33 per cent) of 27 patients, in whom treatment had been stopped, subsequently remained essentially normotensive for between six months and five years. In a later review of 65 patients, however, the same authors (Dustom et al., 1968) found that diastolic hypertension reappeared in all but two patients. Thurm and Smith (1967) investigated 69 patients with mild to moderate hypertension. They found that 16 (23 per cent) remained normotensive for periods of 10 to 42 months. The Veterans Administration Study Group (1975) reported a 15 per cent remission in 60 patients followed for 18 months. The mean diastolic pressure in this group was 109 mmHg. In all these trials, the initial control of blood pressure had involved the use of a variety of drugs, usually in combination.

If the level of blood pressure could be maintained at the lower levels reached during treatment, it was logical to assume that, once treatment was stopped, the lower levels would probably be maintained in those individuals who had not been severely hypertensive before starting treatment, and in whom only a simple therapeutic regime was required to control hypertension.

We therefore decided to investigate the effect of withholding treatment from a group of patients with mild hypertension in all of whom the hypertension had been well controlled by thiazide diuretics only.

Only those patients without complications of a raised arterial pressure were included in the trial; some had already been included in the treatment group of a controlled trial of treatment of mild hypertension (Baillie Johnson et al., 1978).

Method

Therapy was withdrawn from 20 patients aged 34 to 68 years (mean 51 years), 9 male and 11 female. All had pre-treatment diastolic pressure in excess of 100 mmHg measured on two or more occasions, the mean pre-treatment blood pressure being 171/111 with a systolic range from 140 to 220, and diastolic range from 100 to 130 mmHg. Only patients whose hypertension had been well controlled (diastolic blood pressure consistently below 100 mmHg) by thiazide alone for two years or more were included. Patients with heart failure, rheumatic heart disease or recent stroke were excluded.

Follow-up was at two weeks, four weeks, three months, and every three months thereafter.

Patients were returned to therapy if the diastolic pressure exceeded 100 mmHg (confirmed by repeated measurements at two-weekly intervals).

Blood pressures were measured using a standard sphygmomanometer. The diastolic pressure was taken at the fourth Korotkow sound.

Thirteen patients had received hydroflumethiazide in conventional doses, two hydrochlorothiazide, two cyclopenthiazide, and three bendrofluazide.

Results

Eighteen patients (9 female, 9 male) were returned to treatment after 1 to 132 weeks (mean 31 weeks). Two women have remained off treatment for 38 and 95 weeks.

There were no obvious features to distinguish these two from the remaining 18 patients, except that both had very mild hypertension before starting treatment. In both, the initial indication for treatment had been their inclusion in a therapeutic trial of treatment of mild hypertension, and in neither would treatment otherwise have been introduced for the conventional indications existing at the time the treatment was started. The level of blood pressure in these two, while taking diuretics, was no different from that of the other patients, the mean being 151/85 in the two, and 136/88 in the 18 in whom treatment had to be resumed.
Although the level of blood pressure has risen in both patients since withdrawal of treatment, in neither has the level of diastolic pressure been maintained consistently over 100 mmHg.

Eighteen patients had essential hypertension. One patient among those returned to treatment had pyelonephritis; another had presented initially with pre-eclamptic toxemia, the hypertension persisting after delivery, and no underlying cause being discovered.

In those resuming treatment there was no apparent association between the rate of return to treatment and age or pre-treatment diastolic pressure.

There was no consistent pattern of weight change in any patient.

Discussion

Despite deliberately selecting a group of patients with mild, simply controlled hypertension, we found that 90 per cent had to return to active therapy.

Whatever the mechanism by which thiazide diuretics reduce blood pressure may be, the only distinction between the majority and the two patients in whom therapy has not yet been resumed is that the two were only mildly hypertensive before starting treatment. It is, of course, possible that in time both will have to resume treatment.

From the practical point of view, there appears at present to be no simple way of detecting hypertensive patients who might remit after a period of treatment, or of knowing how long that remission will persist. The only way of finding out would be to withdraw therapy from patients after a period of effective treatment. Such a measure would obviously involve close monitoring of blood pressure, possibly by the patient himself. Otherwise, adequate management of even mild hypertension must remain continuous, life-long therapy.

This trial indicates quite clearly that, in some patients at least, therapy could be intermittent. However, while in theory this could be an advantage, it is clearly not a practical suggestion, as the introduction of a time-table into intermittent therapy would make the treatment more difficult to maintain and so increase the numbers defaulting from therapy, and from the routine supervision essential after withdrawal of that therapy.

The trial raises one further practical issue with respect to therapeutic trials. The conventional cross-over trial is one in which treatment A is given for a fixed period of time, followed by an interval, usually of 2 to 4 weeks, in which no treatment is given. Treatment B is then introduced and the two treatments are compared.

The very long delay between withdrawal of treatment, and the need for its reintroduction, in some individuals exceeding two years, which we have observed in this trial, certainly casts some doubt upon the validity of such observations.

References
Bailie Johnson, H., Pearce, V. R. and Hamilton, M. (1978) Journal of the Chronic Diseases, 31, 513.

Dustan, H. P., Page, I. H., Tarazi, R. C. and Frohlick, E. D. (1968) Circulation, 37, 370.
McCubbin, J. W., Green, H. J. and Page, I. H. (1956) Circulation Research, 9, 205.
Page, I. H. and Dustan, H. P. (1963) Circulation, 25, 435.
Thurm, R. H. and Smith, W. M. (1967) Journal of the American Medical Association, 201, 301.
Veterans Administration Co-operative Study Group on Antihypertensive Agents (1975) Circulation, 51, 1107.

The First Medical Register

The first medical register was published by J. Murray, bookseller of Fleet Street, in 1779. So it is the bicentenary of this smart bit of private enterprise, so long before there were any such things as registrable qualifications. The register used the various lists of doctors, surgeons and apothecaries that were available. Fellows of the College of Physicians did well, as their entries included their address in London and their main publications. Licentiates just got listed but the more prominent surgeons had a fuller entry. Each London hospital had a descriptive paragraph, mostly to show their benefactors; their medical staffs were also reported. England as a whole was covered by a list of physicians, surgeons and apothecaries in each county. County hospitals and local medical societies were included. There were also lists of those serving in the army and navy. In short, this first register is a gold-mine for the historian. Much of it was compiled by correspondence, asking for names. Of the hundred or so practitioners approached for help, only three objected to 'the propriety and usefulness of the plan'. If favourably received it was hoped to make it an annual publication. Indeed a second edition came out in 1780 but the third and last edition appeared in 1783.

The register was the brain-child of Dr Samuel Foart Simmons, son of the town clerk of Sandwich, Kent. Educated in a French seminary, he studied medicine in Edinburgh and proceeded to MD Leyden in 1776. He made a leisurely and personally successful tour of medical centres in Germany and Switzerland, visiting Voltaire at Ferney. Settling into a London practice with the licence of the College in 1778, his career had a vertical take-off. Three years later he was a Fellow of the Royal Society, physician to the Westminster General Dispensary and to St Luke's Hospital, had published two editions of his medical directory, had founded and was editing the London Medical Journal and was rapidly accumulating a fortune from his private madhouse. His skill in handling mental disease meant that he was called to treat George III in 1803, and in 1811 was one of the doctors giving evidence before the House of Commons on the return of the king's insanity. Curiously, Simmons wrote books on the treatment of consumptions, gonorrhoea and the tape worm, but nothing on madness.