FIRST EXPERIENCES WITH A NEW ANTI-HYPERTENSIVE AGENT 'DARENTHIN'

ROY MORRIS, M.D., M.R.C.P.E., *Johannesburg*

That the long-term management of severe hypertension is far from satisfactory will be abundantly clear to most practitioners. The indications for treatment, as well as the lack of unanimity which exists, are put forth succintly in a recent masterly review of the subject by Turner.[1,2]

With the advent of the ganglion-blocking agents it appeared that 'medical sympathectomy' had become possible. Experience soon showed, however, that in the majority of cases the treatment was worse than the disease, and patients preferred to suffer the relatively minor symptoms of their disorder rather than the persistent agony of the toxic effects of drugs (dry mouth, severe constipation, visual disturbances, difficulty in urinating, impotence, lassitude, etc.).

In the United States of America there was a swing away from ganglion blockade towards older drugs such as hydrallazine and veratrum, and surgical sympathectomy remained in favour.

A new impetus has been given to therapy with the advent of chlorothiazide and its derivatives, combined with previously used drugs. This served not only to increase the anti-hypertensive effects, but also to increase the cost of treatment and to add new side-effects.

Shortly after the publication of a promising report by Boura *et al.*,[3] the manufacturers of Darenthin were kind enough to let me have a trial supply.

Darenthin (bretylium tosylate), briefly, is a drug which accumulates selectively in the sympathetic ganglia, postganglionic sympathetic fibres and, in general, in those organs with a rich adrenergic innervation, thereby decreasing vascular tone. This effect may be reversed by the administration of adrenergic substances. It appears that only the noradrenaline produced locally at nerve endings is inhibited.

THE TRIAL

So far 7 patients have received the drug for periods varying from 21 to 70 days. The conditions of the trial were uncontrolled, and are just those which obtain in everyday practice. No patient was given bed rest, and everyone went about his usual occupation. Blood pressures in all instances had been recorded many times before treatment began, and were checked daily after its commencement, usually about 2 hours after a dose of the drug had been taken. Pressures were recorded after the patient had been standing for *at least* 2 minutes. Due to the mode of action of Darenthin, there is no point in recording a recumbent blood pressure as it will necessarily be in the pre-treatment region.

Case 1

Miss W., aged 14, has chronic glomerulonephritis with albuminuria, fundal exudates, left ventricular hypertrophy and a blood pressure of 200/130 mm. Hg (fixed). The blood urea was 28 mg.%, maximum urinary concentration 1,020 and the excretion on intravenous pyelography was good. She was given reserpine and ganglion blockade with a drop in the standing blood pressure to 155/100 mm. Hg, but she complained of visual difficulty and nausea. On 5 October 1959, Darenthin was commenced, using 600 mg. daily. A week later the blood pressure was 130/85, and again a week later 150/105 mm. Hg. The dose was increased to 1 g. daily without affecting the blood pressure significantly, but no side-effects were noted.

Case 2

Mr. J., aged 46, suffers from malignant hypertension as evidenced by gross albuminuria, marked left ventricular hypertrophy with a strain pattern on the ECG, visual symptoms and a small patch of exudate in one fundus.

The pre-treatment blood pressure was about 240/150 mm. Hg and a good response could be obtained with reserpine, a ganglion blocker, and chlorothiazide. He felt, however, that life under these conditions was not worth living and ultimately stopped treatment of his own accord and consulted a naturopath. He returned to me feeling very well indeed, but his blood pressure was 240/160 mm. Hg. Darenthin was administered, starting on 600 mg. daily. He complained of some looseness of the bowels and transient stuffiness of the nose as well as tiredness. Daily blood pressure recordings were as follows: 190/140, 160/130, 140/110 mm. Hg. The dose was increased to a maximum of 2 g. daily, at which stage he fainted one morning. A reduction to 1,600 mg. daily has given reasonable control between 120/90 and 130/95 mm. Hg. This patient complained so much of lethargy that the drug was stopped for 3 days, after which he said he felt well, but the blood pressure had risen to 190/150 mm. Hg. Treatment is being recommenced.

Case 3

Mrs. S., aged 55, hypertensive for 6 years at least, had received all the usual forms of therapy with unpleasant side-effects and discontinued all treatment a week before the consultation. Her blood pressure at rest was 200/130 mm. Hg; an auricular gallop was present, and arteriovenous nicking in the optic fundi, as well as spasm and irregularity of the vessels. ECG within normal limits, urine free of albumin and sugar. Noteworthy was the fact that two sisters died of the sequelae of hypertension, and one sister, alive, has hypertensive heart disease.

On 600 mg. of Darenthin daily the blood pressure fell to 115/80, and then rose to 200/130 and 180/120 mm. Hg. The dosage was increased to 1,200 mg. and subsequent pressures have been 130/80, 145/95 and 125/85 mm. Hg. There have been no side-effects.

Case 4

The pre-treatment blood-pressure levels of Mr. B., aged 50, averaged 235/150 mm. Hg. Treatment with other drugs had brought it down to about 185/115 mm. Hg, with slight side-effects from the drugs. He was given Darenthin 100 mg. *t.d.s.*, and on the second day he fainted. About an hour later the systolic blood pressure was 70 mm. Hg. After this he *appeared* to become resistant to the drug, so his doctor built up the dosage to a total of 1,800 mg. daily. At this stage the patient complained of dizziness and said he did not feel well. The reason for this becomes apparent from the following blood pressure readings: Erect, after 3 minutes the blood pressure was 155/110, at 5 minutes 130/100, and at 7 minutes 110/90 mm. Hg. At that time dizziness appeared and no doubt further immobile standing would have produced an even greater fall.

This illustrates one of the difficulties in adjusting the dose, for this patient was being overdosed and casual blood pressure recordings indicated just the opposite.

Case 5

Mrs. C., aged 50. Long-standing malignant hypertension in the region of 250/130 mm. Hg. She responded to ganglion blockers with a pressure of 180/80 mm. Hg, with marked toxic effects. After 10 days on Darenthin, 800 mg. daily, her blood pressure was 200/90 mm. Hg and there were no side-effects. After about 10 days she appeared to become resistant to the drug and the blood pressure rose to 220/130 mm. Hg. The dosage was not increased, and then, as signs of congestive failure appeared, the drug was stopped. The patient had been in failure previously. This case does not represent a fair trial of the drug.

Case 6

Mrs. M., aged 47, had been hypertensive for many years, the blood pressure being in the region of 250/120 mm. Hg. She

had always had tachycardia. She had taken reserpine for 4 years without much effect, and could not tolerate ganglion-blocking agents. This patient's blood pressure, owing to a misunderstanding, had always been measured in the sitting position, averaging 180/100 mm. Hg on 600 mg. of Darenthin daily. Very likely a standing blood pressure would have given lower figures representing adequate control. It is of interest that her tachycardia has disappeared and she reports feeling better than before.

Case 7

A medical practitioner, aged about 45, had been severely hypertensive for many years with an untreated blood-pressure level of 260/160 mm. Hg. His blood urea was 51 mg.%. He had been treating himself with hydrallazine, reserpine, and ganglion-blocking agents, but suffered severe and distressing side-effects.

He commenced taking Darenthin, 600 mg. daily, and the blood pressure came down to 180/110 mm. Hg. The dosage was then gradually increased to a total of 1,600 mg. daily without much improvement. It was therefore lowered again to 600 mg. daily, and dichlorothiazide, one tablet, was taken every alternate day. It has been noted that after taking the dichlorothiazide the blood pressure falls to about 100/70 mm. Hg and then gradually rises over the next 48 hours. This patient is delighted with the results and absence of toxic effects of his new treatment.

DISCUSSION

Darenthin is an effective antihypertensive agent and appears to be free of toxicity. One patient complained of a blocked nose, but this passed off and may not have been due to the drug. A few have noted some tiredness and say they sleep abnormally well. Two patients have had postural faints. In one case the systolic blood pressure an hour later was 70, and in the other case 80 mm. Hg.

The drug acts fully only when patients are in the erect position, partially when sitting, and hardly at all when recumbent. It remains to be seen whether sufficient protection can be given to a hypertensive patient during his standing hours to safeguard him from the effects of the disorder, or whether it will be advisable to use, in combination, some drug which affects the blood pressure in recumbency (probably a drug with a central site of action).

There is no doubt that the advent of bretylium tosylate marks a major advance in the treatment of hypertension, and is the forerunner of further progress.

CONCLUSIONS

1. Seven hypertensive patients have been treated with bretylium tosylate (Darenthin).

2. At one time or another the drug lowered the blood pressure significantly in all cases, even to the point of fainting.

3. Some patients seem to develop a 'resistance' to the drug, but it is felt that this is more apparent than real and is probably due to a faulty technique in recording the blood pressure.

4. Darenthin, in the doses used, is quite free of serious side-effects.

5. Care must be taken, when adjusting the dosage, that the minimum blood pressure reading is obtained, and for this the patient should be allowed to stand for several minutes.

6. It is possible that the addition of small doses of chlorothiazide-like drugs will iron out many of the problems of treatment with Darenthin.

ADDENDUM

Case 1

This patient's blood pressure has remained in the region of 150/100 mm. Hg. No side-effects have occurred and the heavy exudates in the fundi have all but cleared.

Case 2

Much of this patient's symptomatology can be attributed to renal dysfunction, for a recent blood-urea estimation gave a figure of 110 mg.%, with a serum potassium of 3·1 m.Eq./l. After recommencement of treatment, control of the blood pressure has remained very satisfactory, in the region of 130/90 mm./Hg.

Case 3

This patient seems to have developed resistance to the drug. On 1,600 mg. daily, supplemented with a daily dose of 50 mg. of Esidrex, her standing blood pressure remains in the region of 170/110 mm. Hg. Reserpine has been added, and the administration of Esidrex stopped. She insists, however, that she has never felt better and has developed the ability to sleep soundly. This has been mentioned by other patients too.

Case 7

A repeat blood urea on the patient showed a drop from 51 to 43 mg.% since the institution of Darenthin therapy.

Case 8

Since originally writing this paper, one further patient has been on treatment for over 1 month. She is a lady aged 50, who has had marked uncomplicated hypertension for many years, culminating in severe headaches and incapacitating vertigo. Treatment with reserpine, chlorothiazide and a ganglion-blocking agent was given, but the patient felt miserable and was unwilling to cooperate. Her treatment was then changed to Darenthin without supplementary medication and her blood pressure has remained between 130/80 and 150/100 mm. Hg. The pre-treatment level was about 240/150 mm. Hg.

On 1,200 mg. of Darenthin daily her blood pressure fell to 80 systolic and she complained of weakness and dizziness. The dose was therefore reduced to 800 mg. with a resulting slight rise in pressure and abolition of symptoms.

I should like to thank Mr. B. Cuppelditch, of Burroughs Wellcome & Co. (South Africa) Ltd., for generous supplies of Darenthin, and my colleagues for information on patients under their care.

REFERENCES

1. Turner, R. W. D. (1959): Lancet, **1**, 897.
2. *Idem* (1959): *Ibid.*, **1**, 953.
3. Boura, A. L. A. *et al.* (1959): *Ibid.*, **2**, 17.