insufficiency, but adolescence, when a growth spurt should occur, coincides with the very time that the majority reach the stage of terminal renal failure. Furthermore, the corticosteroid therapy which renal transplantation necessitates may also retard optimum growth. The degree of catch-up growth that is possible in these children remains to be determined.

We suggest that careful attention should be given to the dietary intake of energy and nutrients of all infants with renal insufficiency in an attempt to prevent growth retardation during this vulnerable period. It therefore follows that if such a dietary programme is to be successful in achieving normal growth the detection of chronic renal insufficiency in infancy is of paramount importance. In older children, once failure to thrive and growth retardation have occurred the opportunity to promote catch-up growth may be lost.

This work was supported by Medical Research Council grant No. G 972/143/C. We thank Dr. R. H. R. White, under whose care these patients were investigated, and Dr. P. Rayner for their helpful criticism and advice.

Requests for reprints should be addressed to Dr. P. R. Betts, The Children's Hospital, Ladywood Middleway, Birmingham B16 8ET

References

Ashworth, A. (1968). *British Journal of Nutrition*, 22, 341.
Ashworth, A., Bell, B., James, W. P. T., and Waterlow, T. C. (1968). *Lancet*, 2, 600.
Chantler, C., and Barratt, T. M. (1972). *Archives of Disease in Childhood*, 47, 613.
Chantler, C., Adelman, R. D., MacDonell, R. C., and Holliday, M. A. (1973). Paper read at the Paediatric Research Society, October.
Chantler, C., and Holliday, M. A. (1973). *Clinical Nephrology*, 1, 230.
Coles, G. A. (1972). *Quarterly Journal of Medicine*, 41, 25.
Cook, J., *et al.* (1973). *British Journal of Preventive and Social Medicine*, 27, 91.
Dent, C. E., Harper, C., and Philpot, O. R. (1961). *Quarterly Journal of Medicine*, 30, 1.
Department of Health and Social Security (1968). *Pilot Study of Nutrition of Young Children in* 1963. London, H.M.S.O.
Department of Health and Social Security (1969). *Recommended Intakes of Nutrients for the United Kingdom*. London, H.M.S.O.
Dreizen, S., Spirakis, C. N., and Stone, R. E. (1967). *Journal of Pediatrics*, 70, 256.
Glasgow, E. F., Moncrieff, M. W., and White, R. H. R. (1970). *British Medical Journal*, 2, 687.
Greulich, W. W., and Pyle, S. I. (1959). *Radiographic Atlas of Skeletal Development of the Hand and Wrist*, 2nd edn. California, Stanford University Press.
Krueger, R. H. (1969). *Lancet*, 2, 514.
McCance, R. A., and Widdowson, E. M. (1967). *Medical Research Council Special Report Series*, No. 297. London, H.M.S.O.
Reimold, E. W. (1973). *Pediatrics*, 52, 235.
Simmons, J. M., Wilson, C. J., Potter, D. E., and Holliday, M. A. (1971). *New England Journal of Medicine*, 285, 653.
Tanner, J. M., Whitehouse, R. H., and Takaishi, M. (1966). *Archives of Disease in Childhood*, 41, 454, 613.
West, C. D., and Smith, W. C. (1956). *American Journal of Diseases of Children*, 91, 460.
Widdowson, E. M. (1970). *Lancet*, 1, 901.
Wills, M. R. (1971). *Biochemical Consequences of Chronic Renal Failure*, p. 54. London, Harvey, Miller and Medcalf.

Deterioration in Renal Function after Beta-blockade in Patients with Chronic Renal Failure and Hypertension

DAVID J. WARREN, C. P. SWAINSON, N. WRIGHT

British Medical Journal, 1974, 2, 193-194

Summary

Treatment of hypertension with beta-blocking agents in three patients with moderately severe chronic renal failure was followed by rapid deterioration of renal function. In two of the patients the need for maintenance haemodialysis was accelerated but renal function in the third reverted to pretreatment levels after the drug was stopped. These findings suggest that until more is known about the effects of beta-blocking drugs they should not be given to patients with moderately severe renal failure.

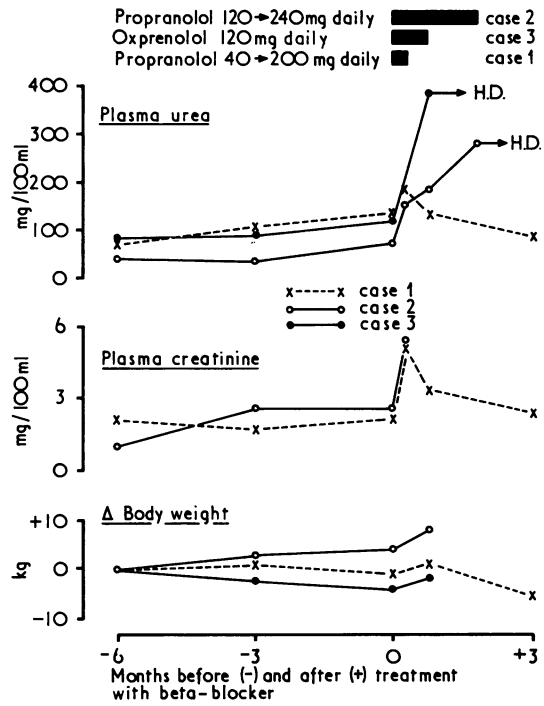
Introduction

Beta-adrenergic receptor blocking agents (beta-blockers) have a proved place in the management of patients with hypertension. Their use in large numbers of patients has shown that they do not cause deterioration of renal function, even in patients with pre-existing mild renal failure (Pritchard and Gillam, 1969; Lydtin *et al.*, 1972). It has been suggested that a beta-blocker given together with a vasodilator might be the treatment of choice for hypertension complicating chronic renal failure (*British Medical Journal*, 1973). We report three patients with chronic renal failure and hypertension whose renal function greatly deteriorated after beta-blockade.

Medical Renal Unit, Department of Medicine, Royal Infirmary, Edinburgh EH3 OYW
DAVID J. WARREN, B.M., M.R.C.P., Lecturer
C. P. SWAINSON, M.B., Senior House Physician
N. WRIGHT, M.B., M.R.C.P., Senior Registrar

Case Reports

The patients in two of the cases (cases 2 and 3) were referred to the unit after renal function had deteriorated. The results of biochemical and blood pressure investigations were obtained from



Plasma urea and creatinine concentrations and body weight before and after initiation of antihypertensive therapy with beta-blockers. Rectangular bars indicate duration of beta-blocker treatment. H.D. = haemodialysis.

the case notes in all patients. Renal function and body weight for six months before and up to three months after beginning beta-blockade are shown in the fig.

Case 1.—The patient, a 37-year-old turf accountant, was found on renal biopsy in 1966 to have mesangiocapillary glomerulonephritis. His blood pressure was 130/90 mm Hg supine. By 1967 his blood pressure had risen to 150/100 mm Hg supine and he was treated with methyldopa. When admitted to hospital for renal biopsy in February 1973 his blood pressure was 160/110 mm Hg supine and 110/80 mm Hg erect. There was no clinical or radiological evidence of cardiac enlargement and an E.C.G. was normal. The plasma urea was 120 mg/100 ml and plasma creatinine 2·1 mg/100 ml. To try to control the blood pressure without producing postural symptoms 40 mg daily of oral propranolol was prescribed. After nine days the dose was increased to 200 mg daily. The blood pressure during this period was 140/90 mm Hg supine and 120/80 mm Hg erect. The plasma urea rose to 184 mg/100 ml and plasma creatinine to 5·4 mg/100 ml. Propranolol was withdrawn and the plasma urea and creatinine concentrations fell to pretreatment levels. Throughout this period the patient was given his normal daily dose of allopurinol and indomethacin.

Case 2.—This was a 33-year-old lorry driver who was found on renal biopsy in 1968 to have chronic nephritis. At that time his blood pressure was 140/110 mm Hg supine. Chest *x*-ray film and E.C.G. were normal. The plasma creatinine was 0·8 mg/100 ml and plasma urea 40 mg/100 ml. His hypertension was treated with methyldopa and bendrofluazide. In January 1973 he was admitted to hospital with chest pain. No evidence of myocardial infarction or cardiac failure was found. His blood pressure on discharge was 160/110 mm Hg supine, blood urea was 81 mg/100 ml, and creatinine 2·6 mg/100 ml on an unrestricted diet. To improve blood pressure control oral propranolol was started at a dose of 120 mg daily two weeks after discharge and increased to 160 mg daily two weeks later, when his supine blood pressure was 150/100 mm Hg. There was no clinical or radiological evidence of cardiac failure but his blood urea had risen to 150 mg/100 ml. After 14 days the dose of propranolol was increased to 240 mg daily when the supine blood pressure was 160/100 mm Hg. The blood urea had risen to 170 mg/100 ml and creatinine to 5·4 mg/100 ml. Six weeks later he was admitted to hospital with pulmonary oedema. The supine blood pressure was 180/105 mm Hg, plasma urea 281 mg/100 ml, and creatinine 13·0 mg/100 ml. Withdrawal of propranolol and institution of conservative therapy failed to restore renal function and he was established on maintenance haemodialysis.

Case 3.—A 33-year-old labourer was admitted to hospital in November 1971 with hypertension, left ventricular failure, and chronic renal failure. At the time of discharge his blood pressure was 200/100 mm Hg supine and 130/110 mm Hg erect. There was no clinical or radiological evidence of cardiac failure; the plasma urea concentration was 69 mg/100 ml, plasma creatinine 2·1 mg/100 ml, and endogenous creatinine clearance 37 ml/min. He remained well; cardiac failure and hypertension were controlled by digoxin, bendrofluazide, potassium supplements, and debrisoquine. By January 1973 his blood urea had risen to 132 mg/100 ml, and his sitting blood pressure was 180/100 mm Hg. Oxprenolol was started as an adjunct to the antihypertensive therapy in a dose of 120 mg daily by mouth. He was admitted to hospital 20 days later in severe renal failure and with pulmonary oedema. The blood pressure was 210/110 mm Hg supine and the plasma urea 380 mg/100 ml. Oxprenolol was discontinued and the blood pressure controlled by larger doses of debrisoquine. Renal function did not improve with conservative treatment and maintenance haemodialysis became necessary.

Discussion

Renal function in each of these patients deteriorated after treatment with beta-blocking drugs. In two the deterioration was severe and irreversible and necessitated the institution of maintenance dialysis before it might otherwise have been required. In the patient (case 1) in whom the deterioration was reversible the beta-blocker had been given for only nine days compared to 20 days and 70 days in the other two patients. There was no evidence of infection, oligaemia, or exposure to nephrotoxic drugs to cause the deterioration, nor did it follow an episode of malignant hypertension or myocardial infarction. Only one patient had had a previous episode of heart failure, and this was controlled when beta-blockade was begun.

Despite the negative inotropic and chronotropic effects of intravenous propranolol (Stephen, 1966) the full antihypertensive effect of oral propranolol may not be achieved until several weeks after therapy is begun (Pritchard and Gillam, 1969), and it is associated with a sustained fall in peripheral resistance and cardiac output (Terazi and Dunstan, 1972). Beta-blockers possessing intrinsic sympathomimetic activity have been advocated in the belief that they would be less likely to precipitate cardiac failure. Nevertheless, practolol may have negative chronotropic and inotropic effects in patients with heart failure well-controlled by digitalis (Sowton *et al.*, 1968), and oxprenolol has negative chronotropic effects in normal subjects (Choquet *et al.*, 1972).

Cardiac output was not measured in our patients, but probably the deterioration in renal function was due to reduced renal blood flow as a result of a reduced cardiac output. Glomerular filtration rate is reduced by propranolol and oxprenolol in hypertensive patients with normal renal function (Bufano and Piacentini, 1969; Schirmeister *et al.*, 1969). Propranolol also reduces renal blood flow (Nayler *et al.*, 1967) and glomerular filtration rate in hypertensive patients after two-three months of treatment (Ibsen and Sederberg-Olsen, 1973). Ibsen and Sederberg-Olsen (1973) suggested that the reduced glomerular filtration rate in hypertensive patients with normal renal function was not of functional significance. A reduction in filtration rate in patients with chronic renal failure may produce a considerable rise in plasma urea and creatinine. Further studies are needed to clarify the effects of beta-blockers on renal function in patients with renal failure.

Since renin secretion seems to be under the control of a beta-receptor mechanism it has been suggested that reduction of the hypertension in patients shown to have high plasma renin activity might be achieved by beta-blockade (Buhler *et al.*, 1972). The fact that secretion of renin is relatively autonomous in patients with chronic renal failure (Warren and Ferris, 1970) renders this hypothesis less likely in this group of hypertensive patients.

Recent evidence suggests that the urinary excretion rate of metabolites of ^{14}C propranolol is greatly reduced in patients whose creatinine clearance is less than 35 ml/min (Thompson *et al.*, 1973). If these metabolites possess beta-blocking properties the sensitivity of patients with chronic renal failure to them may be increased. Our experience suggests that beta-blocking drugs should not be given to patients with moderately severe renal failure.

Requests for reprints should be addressed to Dr. D. J. Warren.

References

British Medical Journal, (1973). **4**, 185.
Bufano, G., and Piacentini, L. (1969). *Minerva Medica*, **60**, 1229.
Buhler, F. R., Laragh, J. H., Baer, L., Vaughan, E., and Brunner, H. R. (1972). *New England Journal of Medicine*, **287**, 1209.
Choquet, Y., Capone, R. J., Mason, D. T., Ezra, A. A., and Zelis, R. (1972). *American Journal of Cardiology*, **29**, 257.
Ibsen, H., and Sederberg-Olsen, P., (1973). *Clinical Science*, **44**, 129.
Lydtin, H., *et al.* (1972). *American Heart Journal*, **83**, 589.
Nayler, W. G., McInnes, J., Swann, J. B., Carson, V., and Lowe, T. E. (1967). *American Heart Journal*, **73**, 207.
Pritchard, B. N. C., and Gillam, P. M. S. (1969). *British Medical Journal*, **1**, 7.
Schirmeister, J., Decot, M., Hallover, W., and Willman, H. (1966). *Artzneimittel Forschung*, **16**, 847.
Sowton, E., Balcon, R., Cross, D., and Frick, H. (1968). *British Medical Journal*, **1**, 215.
Stephen, S. A. (1966). *American Journal of Cardiology*, **18**, 463.
Terazi, R. C., and Dunstan, H. P. (1972). *American Journal of Cardiology*, **18**, 463.
Thompson, F. D., Joekes, A. M., and Foulkes, D. M. (1973). *American Heart Journal*, **85**, 427.
Warren, D. J., and Ferris, T. F. (1970). *Lancet*, **1**, 159.