THE EFFECT OF ORAL DIAZOXIDE ON HYPERTENSION AND SODIUM EXCRETION IN CHRONIC RENAL FAILURE

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SUMMARY

1. Oral diazoxide was administered to a group of ninety-seven patients with renal failure and severe hypertension which had proved resistant to conventional drug treatment.

2. Hypertension was satisfactorily controlled in every case, and resistance to therapy did not occur.

3. Creatinine clearance showed a minor fall in the first week of treatment; however, by 3 months a significant improvement in renal function had occurred. This improvement was maintained at 6 months in the patients with primary hypertension and chronic pyelonephritis. In the chronic glomerulonephritic hypertensive patients, however, creatinine clearance was slightly lower at this stage.

4. Sodium retention was a conspicuous feature and required large doses of diuretics.

5. We suggest that vasodilatation leads to imbalance between filling pressure and capacity, so that volume receptors are stimulated. In addition, the decreased arteriolar resistance will lead to increased hydrostatic pressure in the capillary bed, and thus to increased fluid transudation.

Key words: hypertension, diazoxide, creatinine clearance, sodium excretion.

Severe hypertension associated with renal impairment requires urgent treatment if further renal deterioration is to be avoided. Although conventional treatment frequently produces an improvement in renal function (Woods & Blythe, 1967), a substantial minority of patients cannot be controlled satisfactorily, or only achieve acceptable supine blood pressures at the expense of disabling postural hypotension. A previous study suggested that improvement in renal function could be obtained in such patients with the use of long-term oral diazoxide.

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PATIENTS AND METHODS

Ninety-seven patients with severe hypertension were treated for 3–36 months with oral diazoxide (50–800 mg daily). Four main diagnostic sub-groups could be delineated by using conventional clinical, radiological and histological criteria; primary malignant hypertension (i.e. hypertension with papilloedema) (forty-three), chronic glomerulonephritis (twenty-four), chronic pyelonephritis (fourteen), and others including essential hypertension, renal artery stenosis, polycystic kidney disease, scleroderma and amyloid disease (sixteen). Small doses of methyldopa or debrisoquin were also given as adjuvants. Each patient was instructed to carry out daily urine testing for sugar with Clinitest tablets. Blood sugar estimations were carried out twice daily during the time spent in hospital and at each subsequent out-patient visit. Gross oedema due to diazoxide-induced sodium retention was prevented by the use of large doses of frusemide or ethacrynic acid.

One patient was given a fixed sodium diet in the metabolic ward and a full sodium balance obtained for a 14 day period.

Blood pressure measurements were made personally by the authors, using a mercury sphygmomanometer. Frequent blood and 24 h urine samples were obtained from all patients. Creatinine was measured on a Technicon auto-analyser, sodium and potassium by flame photometer.

RESULTS

The mean blood pressure of the ninety-seven patients was 228±(SEM) 3·2 mmHg systolic and 149±1·8 mmHg diastolic before diazoxide was administered. Creatinine clearance values were available for forty-nine patients on first presentation. The mean clearance for this group was 38·6±4·14 ml/min. The patients were managed on conventional agents for up to several years. By the end of this period mean creatinine clearance showed a fall of 17·2±2·0 ml/min.

Hypertension responded satisfactorily to oral diazoxide in every case, resistance to therapy not being observed. Group mean blood pressures were calculated over 3 month intervals from the third to the thirtieth month. During hypotensive treatment the mean lying blood pressure varied from 155±4·3 mmHg (lowest reading) to 170±3·6 mmHg (highest reading) systolic and 88±2·7 mmHg to 98±1·5 mmHg diastolic. The mean standing blood pressure ranged from 145±6·3 mmHg to 158±4·6 mmHg systolic and 81±1·5 mmHg to 93±1·7 mmHg diastolic.

Many patients showed a fall in renal function during the acute period of blood pressure reduction (day 4 to day 7 of treatment). Detailed studies were made in fifteen patients. Ten patients in advanced renal failure with a mean creatinine clearance of 4·29±0·88 ml/min had a significant fall of 0·62±0·18 ml/min (P<0·05). Five other patients with a mean initial creatinine clearance of 30·3±9·0 ml/min had a non-significant fall of 5·6±6·4 ml/min. With good blood pressure control, however, renal function soon improved, often to above the pre-treatment values. Patients with primary malignant hypertension who had an initial creatinine clearance of 31·9±3·9 ml/min showed significant improvement of 12·9±2·7 ml/min after 3 months' therapy. In the pyelonephritis group the mean clearance of 15·1±5·1 ml/min rose by 7·1±2·7 ml/min.
Glomerulonephritic patients with an initial clearance of $9.9 \pm 2.35$ ml/min showed a mean rise of $2.1 \pm 0.88$ ml/min. All these differences are statistically significant ($P < 0.05$).

Improvement was sustained in patients with primary malignant hypertension and pyelonephritis followed for 6 months or longer. Thus, of the patients with primary malignant hypertension followed for 6 months or more creatinine clearances were available on seventeen. From an initial mean creatinine clearance of $40.6 \pm 7.1$ ml/min clearance rose to $49.3 \pm 8.4$ ml/min at 3 months and $54.4 \pm 8.8$ ml/min at 6 months. Comparable values for five chronic pyelonephritic patients were $24.4 \pm 8.7$ ml/min, $37.0 \pm 16.8$ ml/min and $42.3 \pm 15.7$ ml/min. However, renal function showed no significant change in fifteen chronic glomerulonephritic patients with values of $10.4 \pm 2.3$ ml/min, $12.1 \pm 1.9$ ml/min and $9.8 \pm 2.3$ ml/min. In six of these patients renal function was inadequate to sustain life without special support measures (creatinine clearance < 2 ml/min).

Thirty-one of the ninety-seven patients have been successfully treated for a year and fourteen for over 2½ years; twenty-three patients died while taking diazoxide. Renal failure caused the death of nine patients, pulmonary infection accounted for another four, three died of a
myocardial infarction, two of cerebral infarction and one patient died of a pulmonary embolus. The cause of death in the remaining three patients could not be ascertained.

A fall in urinary sodium excretion occurred in all patients given oral diazoxide. Patients with advanced renal failure had hardly any sodium in the urine and required massive doses (> 250 mg) of frusemide or ethacrynic acid to maintain an adequate urine output and prevent gross oedema developing. Further studies of these patients are presented by Swales, Thurston & Pohl (1972). A patient observed on the metabolic ward, receiving a fixed sodium diet, showed escape from the sodium-retaining action of diazoxide (Fig. 1). At the end of 10 days' treatment the urinary sodium output rose almost to equal the daily sodium intake. Urine sodium concentration rose from 0·85 mmol/l to 21·3 mmol/l, although the patient was still oedematous at this stage.

DISCUSSION

Diazoxide is a uniquely effective therapy for drug-resistant hypertension, given either intravenously (Mroczek, Davidov, Gavrilovich & Finnerty, 1969) or orally (Pohl & Thurston, 1971). The development of tolerance to its hypotensive action has not been observed by us. An almost uniform improvement of renal function occurred in our patients other than those with glomerulonephritis: this was probably mainly due to the adequacy of blood pressure control achieved and maintained. Thus, the mean creatinine clearance of 22·3 ± 2·6 ml/min in our patients improved by 8·7 ± 2·6 ml/min during 3 months' oral diazoxide treatment. The benefit was sustained where primary malignant hypertension was the basic disorder. Pyelonephritics also showed continued benefit, supporting the contention that hypertension in these patients unmask a constitutional predisposition to essential hypertension rather than being a manifestation of the renal disease (Lancet, 1968). Although an initial improvement occurred when glomerulonephritis was the underlying basic disorder, it was not maintained as the disease process progressed.

Diazoxide produces sodium retention which necessitates high dosage diuretic therapy. Mroczek et al. (1969) made a special point of the combination of intravenously administered diazoxide with powerful diuretics to maintain an adequate urine output during treatment. Patients in advanced renal failure show a reduction in urinary sodium concentrations to levels lower than can be normally achieved by prolonged sodium depletion (Swales et al., 1972). It is probable that diazoxide causes increased proximal tubular sodium reabsorption (Pohl, Thurston & Swales, 1972) and therefore a reduced sodium load on the distal tubule. Johnson (1971) suggested diazoxide could have a direct action on the renal tubule. However, diazoxide injected directly into the renal artery causes a natriuresis (Greene, 1967) and we believe the renal sodium action is an indirect one.

Marked sodium retention is a consistent feature of treatment with such vasodilators as hydralazine (Nickerson, 1965), clonidine (Brest, 1969) and minoxidil (Gilmore, Weil & Chidsey, 1970). It has been suggested that decreased arterial filling pressure caused by a change in the relationship between the volume of blood in the arterial tree and the capacity of the arterial vascular bed is a potent stimulus to renal sodium reabsorption (Schrier, Humphreys & Ufferman, 1971). We have suggested that such a mechanism may explain sodium retention during vasodilator therapy (Pohl et al., 1971). A powerful argument against such a hypothesis would be failure of sodium excretion to escape after expansion of the extracellular and plasma
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volumes by a progressively positive cumulative sodium balance. However, our balance study indicates that escape does occur after the development of oedema; so our hypothesis at least does not fall on this basis. Vasodilatation exposes the capillary bed to a raised hydrostatic pressure, causing fluid transudation until a steady-state is reached. Our hypothesis suggests that the development of effective vasodilators in the treatment of hypertension necessarily leads to sodium retention and this will always require concurrent diuretic therapy.

REFERENCES