The effects of two combinations of a beta-blocker and a diuretic on diuresis in normal subjects

DE K SOMMERS, M VAN WYK, H S SCHÖEMAN

Summary
Combinations of a beta-blocker and a diuretic often produce a greater fall in blood pressure than does either drug alone. Furthermore, beta-blockers prevent an increase in plasma renin activity, thereby attenuating diuretic-induced potassium excretion and also the reduction in hypotensive response to the diuretic.

This study was designed to compare the effects of the two fixed-dose combinations atenolol 100 mg plus chlorthalidone 25 mg (Tenoretic; ICI) and sotalol 320 mg plus hydrochlorothiazide 50 mg (Sotazide; B-M) on the pattern of diuresis and the biochemical composition of the urine in normal subjects. These preparations differ mainly in that the plasma half-lives of chlorthalidone and hydrochlorothiazide are 60 hours and 6 hours respectively; the former therefore accumulates when given once daily while the latter does not.

These two preparations were found to have similar effects on the pattern of diuresis and the biochemical values. It is therefore concluded that the relationship between the serum chlorthalidone level and the fall in serum potassium level is in keeping with the flat dose-response curves for the thiazide and phthalimide diuretics.

Patients and methods
Healthy volunteers are most suitable for studying the basic pharmacology of diuretics because important confounding variables can be avoided. A balanced, randomized block design using 16 healthy male volunteers in their early twenties was followed for drug administration. Informed consent was obtained from each participant, and the study was approved by the Ethics Committee of the Glaxo Institute for Clinical Pharmacology. Groups of four volunteers were housed in the Glaxo Institute for 2 days on two occasions. They were kept in the same room at a constant room temperature and were allowed a normal diet without added salt. Fluid intake was not restricted, but no alcohol, coffee or tea was allowed.

Each subject received medication for 16 days from the commencement of the study. Either one tablet of atenolol plus chlorthalidone or two tablets of sotalol plus hydrochlorothiazide was taken orally at 08h00 every morning. After spending 2 days (08h00 on Friday to 08h00 on Sunday) at the Institute, the volunteers continued to take their medication at home until being readmitted to the Institute 12 days later for a further 2 days. Before each admission each subject had to fast from 22h00 the previous evening, and the fast was continued till 10h00, i.e. 2 hours after medication.
On days 1, 2, 15 and 16 all urine passed between 08h00 and 14h00 (6 hours), between 14h00 and 22h00 (8 hours) and between 22h00 and 08h00 the following morning (10 hours) was collected separately. The urine specimens were frozen as early as possible after collection because bacterial contamination may change the urate content. Because of both the high variability in urate measurement and the small changes which had to be detected all specimens were stored frozen until the end of the 16-day period, when all the urate measurements were then performed as a single batch.

Sotalol and chlorthalidone levels were measured to determine compliance.

Results

Urinary volume

The total volume of urine passed on day 1 was compared with that collected on day 15. Similarly, the 24 volumes on days 2 and 16 were compared. The average decrease from day 1 to 15 produced by sotalol plus hydrochlorothiazide (486.9 ml or 22.2%) did not differ significantly from that produced by atenolol plus chlorthalidone over the same period (473.8 ml or 19.5%). Furthermore, the average increase from day 2 to day 16 produced by sotalol plus hydrochlorothiazide (16.3 ml or 0.7%) did not differ significantly from that produced by atenolol plus chlorthalidone over the same period (5.0 ml or 0.2%).

In order to compare the pattern of diuresis and specifically to determine whether nocturia could be a problem, the average volume of urine produced during the last 10 hours of each day was calculated. The average decrease in volume from day 1 to 15 produced by sotalol plus hydrochlorothiazide (-0.6 ml/h or -1.1%) did not differ significantly from the average increase produced by atenolol plus chlorthalidone over the same period (15.4 ml/h or 30.3%). The increase is only significant at \( P < 0.1 \) (Wilcoxon signed rank test). The average increase produced by sotalol plus hydrochlorothiazide from day 2 to day 16 (6.3 ml/h or 10.7%) did not differ significantly from that produced by atenolol plus chlorthalidone over the same period (9.9 ml/h or 16.8%).

Average sodium excretion during the last 10 hours of each day was also calculated. The average decrease produced by sotalol plus hydrochlorothiazide from day 1 to 15 (3.0 mmol/ml or 32.3%) did not differ significantly from that produced by atenolol plus chlorthalidone over the same period (0.6 mmol/ml or 6.8%). Similarly the decreases produced by the two preparations from day 2 to day 16 (0.3 mmol/ml or 3.8% and 1.2 mmol/ml or 13.0% respectively) did not differ significantly.

Serum potassium levels

The average decrease produced by sotalol plus hydrochlorothiazide from day 1 to day 15 (0.21 mmol/l or 5.0%) differed significantly from that produced by atenolol plus chlorthalidone over the same period (0.57 mmol/l or 13.5%) (Mann-Whitney U test, \( P < 0.01 \)). However, the average decreases produced by the two preparations from day 2 to day 16 (0.31 mmol/l or 7.2% and 0.48 mmol/l or 11.3% respectively) did not differ significantly.

Urinary sodium/potassium ratios

These ratios did not change in a consistent manner over the 24-hour collection periods, suggesting that a rebound activation of the renin-angiotensin system and sodium retention did not occur within this period. With sotalol plus hydrochlorothiazide the sodium/potassium ratio decreased from an average of 3.08 on day 1 to 2.86 on day 15. A slight increase occurred from day 2 to day 16. With atenolol plus chlorthalidone the ratio decreased from an average of 3.30 on day 1 to 2.69 on day 15. Similarly, it decreased from an average of 2.97 on day 2 to 2.82 on day 16.

Serum uric acid levels

The average increase produced by sotalol plus hydrochlorothiazide from day 1 to day 15 (0.12 mmol/l or 27.9%) did not differ significantly from that produced by atenolol plus chlorthalidone over the same period (0.08 mmol/l or 19.0%). The average increases produced by the two preparations from day 2 to day 16 (0.06 mmol/l or 14.3% and 0.04 mmol/l or 9.8% respectively) did not differ significantly. However, prolonged administration of both drugs caused a significant increase in serum uric acid levels (Wilcoxon signed rank test: \( P < 0.005 \) in all cases).

Compliance was confirmed by following the serum levels of the drug in each preparation with the longest half-life. The mean values for chlorthalidone rose from 73.71 ng/ml (day 1) and 110.11 ng/ml (day 2) to 224.86 ng/ml (day 15) and 233.25 ng/ml (day 16). The mean values for sotalol on the same days were 1.15 \( \mu \)g/ml, 1.66 \( \mu \)g/ml, 2.08 \( \mu \)g/ml and 2.08 \( \mu \)g/ml.

Discussion

Much information can be gathered by studies in which diuretics are administered repeatedly to healthy subjects. Inconvenience and ethical considerations require that such studies be limited to 1 or 2 weeks of treatment, but within this time changes in plasma potassium and uric acid values are detectable. The maximum fall in serum potassium value produced by the thiazides or chlorthalidone occurs by the end of the 1st week of treatment, and there is little further fall thereafter. A similar pattern has emerged in studies lasting as long as 2 years. No relationship therefore appears to exist between duration of therapy and serum potassium values after initiation of therapy. In contrast, when diuretics are withdrawn the serum potassium value takes several weeks to return to normal. This therefore limits the use of the cross-over technique in studies of diuretics.

The effects of the two \( \beta \)-blocker/diuretic combinations on the pattern of diuresis did not differ significantly with regard to total average 24-hour urine volume or average urine volume and average sodium excretion over the last 10 hours of each day. The actual values for diuresis and natriuresis obtained on the 2nd day of each admission period (i.e. days 2 and 16, on which conditions were more standardized than on the 'run-in' days 1 and 15) demonstrate that renal sodium homeostasis did not significantly diminish the natriuretic response. Furthermore, the urinary sodium/potassium ratios did not change in a consistent manner over the 24-hour collection periods, suggesting that rebound activation of the renin-angiotensin system did not occur within this period of time. It must, however, be pointed out that serum potassium values are increased by \( \beta \)-blockers, this probably being related to the reduction in plasma renin activity and aldosterone values. Diuretic-induced potassium excretion can therefore be attenuated by the \( \beta \)-blockers in the combination preparations. However, the urinary sodium/potassium ratios did tend to decrease by the end of the 2-week period, and the average serum potassium value decreased by between 5.0 and 13.5%. Atenolol plus chlorthalidone tended to produce a more pronounced fall in serum potassium values than did sotalol plus hydrochlorothiazide, but this difference was not significant when the values for days 2 and 16 were compared. The relation between serum chlorthalidone values and the fall in the serum potassium level is therefore in keeping with the flat dose-response curves for the thiazide and phthalimide diuretics.

Both preparations caused significant urate retention, as judged by a rise in serum uric acid values. This is probably due to...
Nutritional value of diets of Blacks in Ciskei


Summary
This dietary study was part of a nutritional status survey carried out at the request of the Ciskeian Government to provide a baseline from which to formulate a nutrition policy. Nutrient intake was assessed by means of a 24-hour recall of food intake and a diet history, recorded for 750 subjects including children aged 6-23 months, 2-3 years and 7-8 years and lactating women. Nutrient intake was evaluated according to WHO standards. The prevalence of inadequate energy intake was high, especially among the 7-8-year-old children. For all age groups protein represented 11% of total energy intake, but was mainly of low quality. Calcium and iron intakes were low in all age groups, especially in lactating women. For all groups the most deficient vitamin was nicotinic acid, followed by riboflavin and ascorbic acid. This deficiency pattern was the result of a diet consisting predominantly of maize.

A number of studies conducted on urban and rural Black South African populations have provided evidence of clinical and biochemical malnutrition with regard to protein and energy,1 calcium, riboflavin and nicotinic acid,2,4 and folate and vitamin B₁₂.4 In a study in Transkei, Groenewald and co-workers4 found low dietary intakes of calcium, riboflavin, nicotinic acid and vitamin C. The need to combat malnutrition by formulating nutrition policies and implementing nutrition guidance programmes has recently received much attention.4 Recognition of this need by the Ciskeian Government led to a survey in which the nutritional status of subjects was assessed by means of clinical, anthropometrical, biochemical and dietary studies. This report deals with the last aspect.

Material and methods
Sample
Respondents (N = 750) were randomly selected from rural areas selected from a census conducted in 1981 by the Ciskeian Government. The sample was stratified to include 75% of rural areas and 25% of urban areas. The sample was randomly selected from a list of 750 villages, each village containing 50 households. A total of 750 subjects were interviewed, 375 from rural areas and 375 from urban areas.

Department of Health and Welfare, Pretoria
M. J. C. RICHTER, B.SC. HONS
A. S. P. SWANEPOEL, M.SC.
National Research Institute for Nutritional Diseases of the South African Medical Research Council, Parowvallei, CP M. L. LANGENHOVEN, B.SC. HONS
Institute for Biostatistics of the South African Medical Research Council, Parowvallei, CP J. J. FERREIRA, M.SC.
South African Institute for Communication Research, Human Sciences Research Council, Johannesburg P. C. J. JORDAAN, D.ED.
South African Bureau of Standards, Pretoria J. P. DU PLESSIS, D.SC.