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Full Length Research Paper

Effects of hydrochlorothiazide and furosemide on creatinine clearance in some hypertensive Nigerians

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Hydrochlorothiazide and furosemide have been reported to alter the glomerular filtration rate (GFR) and possibly the creatinine excretion by the kidneys. Also, therapy with these diuretics, especially in the elderly, can be complicated by volume depletion resulting in prerenal azotemia. Creatinine clearance (Clcr) is considered to be the most accurate test of renal function. Unfortunately, although these diuretics are widely used in the treatment of hypertension and heart failure in the young and elderly Nigerians, their effects on renal function have been poorly investigated. We, therefore, evaluated the effects of treatment with 21-day single daily oral doses of 25 mg hydrochlorothiazide or 40 mg furosemide on Clcr in this prospective randomized study of forty Nigerians with mild to moderate uncomplicated essential hypertension (20 males and 20 females) 32 to 80 years of age and 40 age and sex-matched healthy normotensive controls while on their usual diet. Blood and 24 h urine specimens were collected at baseline and on days 7, 14 and 21. Specimens were assayed for creatinine and the corresponding Clcr for each day was calculated. Analysis of variance did not show a statistically significant effect of the diuretic regimens on Clcr over the period. This study demonstrates that single daily doses of either of these diuretics do not have a significant effect on Clcr over a short-term monotherapy.

Key words: Hydrochlorothiazide, furosemide, creatinine clearance, hypertensive Nigerians.

INTRODUCTION

Since many drugs are partially or totally eliminated by the kidney, accurate estimate of creatinine clearance (Clcr) is crucial to the application of pharmacokinetics in their clinical use. It is known that age-related physiologic changes such as loss in kidney function are accompanied by a reduced capacity of the individual to dispose of renally excreted drugs. Rowe (1976) reported that normal elderly individuals have GFRs significantly less than those of young individuals and this can adversely affect the ability of the kidneys to remove substances from blood into urine. A major complication of hydrochlorothiazide or furosemide therapy is alteration in GFR and volume depletion, both of which can jeopardise renal function, particularly in the elderly (Nies, 1977; Beerman et al., 1977). Clcr which has been used for decades to estimate GFR, monitor response to drug therapy and progression of renal disease, is therefore indicated, especially in the elderly to rule out renal damage, since these drugs are mainly cleared by renal excretion (Coodley, 1983; Pesce and Kaplan, 1987; Leary et al., 1988; Nankivell, 2001).

MATERIALS AND METHODS

Study population and inclusion criteria

Forty patients recently diagnosed of untreated uncomplicated mild to moderate essential hypertension (20 males and 20 females aged

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32 to 80 years), resident in Auchi a sub-urban town in the Niger-Delta area of Nigeria, were recruited for the study between January and June, 2004. A standard pre-tested questionnaire was administered to subjects to obtain background information about their demographic data, family history of hypertension, current medicines if any, educational and social status as well as dietary habits. Eligible subjects had qualifying hypertension of blood pressure (BP) > 160/95 mmHg and ≤ 180/110 mmHg with no identifiable cause of the hypertension.

Exclusion criteria

Subjects who were on concomitant medications for concurrent illnesses including cardiac, renal, hepatic, gastro-intestinal or endocrinologic diseases e.g. (diabetes) as determined from clinical examination and urinalysis were excluded. Equally, also excluded were subjects with history of smoking, alcohol (drug) abuse, mental disorder or hypersensitivity to sulfonamides as well as pregnant women or women on oral contraceptives.

Control subjects

These were 40 age and sex-matched healthy normotensives (20 males and 20 females).

All subjects signed an informed consent form according to the protocol approved by the Medical Ethics Committee of the Ambrose Alli University College of Medicine.

Participants were advised to maintain their usual diet and the entire prospective and randomized study was conducted in an outpatient setting at Osigbemhe Hospital Auchi. None of the subjects defaulted.

Measurement of height, weight and BP

Participants' heights (without shoes) and weights (on light clothing) were determined respectively with a standard scale (Seca model, UK) and a beam balance (Hackman, UK) by the same trained observer. Sitting blood pressure (BP) (systolic and diastolic) readings were taken by the same observer with a standard mercury sphygmomanometer (Riester Diplomat Presameter, Germany) using the subject's left arm (any constricting clothing on the arm was removed) and observing standardized procedures always between 8:a.m and 10:a.m. The mean arterial pressure (MAP) was calculated using the formula MAP= Diastolic BP + $^1/3$ Pulse Pressure. BP measurements were recorded at baseline (day 0) and at 7,14 and 21 days during pharmacotherapy intervention. Results were not disclosed to subjects.

Determination of urine creatinine

On each of the days every participant was requested to collect a 24 h urine sample at baseline and on days 7, 14 and 21. The importance of carefully collecting all urine passed during the period was emphasized. The volume of urine was recorded each day and the creatinine concentration was determined using Jaffe's method (Pesce and Kaplan, 1987), at the Research and Diagnostic Laboratory of Ambrose Alli University College of Medicine.

From the prepared urine sample of each participant, 0.5 ml was measured out in a test tube A, 0.5 ml of standard was also measured out in a test tube B. 3 ml of diluent was added into tube A. 1 ml each of Na tungstate and 2/3 N H_2SO_4 was added to the tube A to precipitate chromogenes. Tube A was then shaken to mix and then left to stand for 10 min. The mixture in tube A was then centrifuged at 4000 rpm for 2 min. 3 ml of supernatant was added to 1 ml of 0.004 N picric acid and 1 ml of 0.25 N sodium hydroxide. The solution was then shaken and allowed to stand at room temperature for 15 min. 12 ml of diluent was added to standard in tube B. Solutions from A and B were read from the colorimeter (spectrophotometer) at 500 nm. The value of serum creatinine was then calculated by simple proportion knowing the value of standard e.g. Concentration of creatinine in urine (mg/dl) = (A sample / B standard) X 2

Determination of serum creatinine

Venous blood was sampled at baseline and at days 7, 14 and 21. From the prepared serum sample of each subject, 0.5 ml was used to determine serum creatinine concentration using Jaffe's Method as already described.

Pharmacotherapy intervention

The 40 normotensives and 40 hypertensives were divided into 2 subgroups of 20 (10 males and 10 females) identified as subgroups A and B for treatment protocols. Subgroups A in controls and hypertensives were instructed to take every morning for 21 days hydrochlorothiazide (ESIDREX^R) 25 mg tablets (National Agency for Food and Drug Administration and Control (NAFDAC) Reg. No. 04-3705 and expiry date August, 2007 manufactured by Novartis pharma SAS. France.). Also, subgroups B (controls and hypertensives) were instructed to take furosemide (FRUMED^R) 40 mg tablet (NAFDAC Reg. No. 04-3275 and expiry date November, 2007, manufactured by Fidson Drugs Ltd, Lagos,Nigeria) for the same period. Participants collected 3 successive 24 h urine samples and together with the 3 blood samples drawn on days 7, 14 and 21, creatinine concentration in each sample was determined.

Compliance was assessed by sporadic visits, pill counts and urine volume measurement.

Calculation of Clcr

Clcr values corresponding to baseline, days 7, 14 and 21 were calculated using the formula:

$$\text{Clcr (ml/min)} = \frac{\text{mg creatinine/dl urine x ml urine/24 h}}{\text{mg creatinine/dl serum x 1440}}$$

Statistical analysis

The data were analyzed as mean ± SEM or mean ± SD (for age, weight and height) and comparative statistics (GraphPad Prism Software UK) were done using one-way ANOVA with Turkey *post hoc* test and $p < 0.05$ was regarded as significant.

RESULTS AND DISCUSSION

Table 1 shows the parameters for the normotensives and hypertensives. The youngest hypertensive was 32 years (female) and the oldest 80 years (male). There was no statistically significant difference between the means of age (58.10 ± 7.84 and 57.10 ± 11.58 years) as well as the body mass index (26.96 ± 4.53 and 25.15 ± 2.34 kg/m^2) in the normotensives and hypertensives, respectively.

Table 1. Baseline parameters of subjects.

Parameter	Normotensives		Hypertensives	
	Range	Mean ± SD	Range	Mean ± SD
Age (years)	33 – 80	58.10 ± 7.84	32 – 80	57.10 ± 11.58
Height (m)	1.56 – 1.72	1.63 ± 0.04	1.50 – 1.80	1.65 ± 0.07
Weight (kg)	56 – 98	71.74 ± 9.02	52 – 85	68.41 ± 6.86
BMI (kg/m^2)	23.01 – 33.13	26.96 ± 4.53	23.11 – 26.23	25.15 ± 2.34
MAP (mmHg)	83.30 – 106.70	93.13 ± 1.37	130 – 136.70	128.50 ± 1.08*
Urine Volume(ml/24h)		1253.0 ± 1433		1410.0 ± 14.30 ***
Male (n)	20		20	
Female (n)	20		20	

Normotensive and hypertensive values are indicated with a significantly higher MAP and urine volume for the hypertensives.
*p < 0.0001; *** p<0.0006; n = 40 per group.
BMI = Body Mass Index; MAP = Mean Arterial Pressure.

Table 2. Effects of hydrochlorothiazide and furosemide on creatinine clearance (ml/min).

Days	Hydrochlorothiazide		Furosemide	
	Normotensives	Hypertensives	Normotensives	Hypertensives
0	114.30 ± 2.24	112.40 ± 5.99	112.80 ± 2.46	111.20 ± 4.46
7	113.40 ± 2.06	110.20 ± 5.05	111.10 ± 2.48	109.60 ± 4.09
14	110.45 ± 1.55	107.50 ± 4.98	109.90 ± 2.18	108.20 ± 4.33
21	105.35 ± 1.58	103.65 ± 4.32	107.30 ± 1.92	105.45 ± 3.36

Hypertensives have lower creatinine clearance values that are not significantly different from controls n= 40 per group.

There was a significantly higher MAP in hypertensives (128.50 ± 1.08 mmHg) than in controls (93.13 ± 1.37 mmHg) with p < 0.0001. Urine volume was equally significantly higher in hypertensives (1410 ± 14.80 mls) than in controls (1253.0 ±14.33 mls), p<0.0006.

Table 2 shows the effects of hydrochlorothiazide and furosemide on creatinine clearance. There was no significant difference in creatinine clearance between hypertensives and normotensives during treatment with both drugs although values in the hypertensives were slightly lower.

Since it is commonly assumed that renal function, and in parallel, the excretion of drugs, may be considerably reduced in the elderly and adversely affected by toxic drugs renally excreted, creatinine clearance has become a useful tool to adapt drug dosages. Although treatment with hydrochlorothiazide and furosemide caused a slight decrease in Clcr in both normotensive and hypertensives in this study, the difference was not statistically significant. This observation shows that the drugs did not significantly adversely affect renal function. Lam et al. (1995) reported that single doses of these diuretics do not have a significant effect on Clcr determination. Similarly, Dey et al. (1996), Fliser et al. (2001), as well as Wienen and Schierok (2001) also reported that Clcr and pharmacokinetics of these diuretics and other renally excreted drugs are not affected in individuals with normal renal function to a clinically significant extent.

However, it is important to note that the characteristic age-related decline in renal function may affect drug response as well as drug disposition. For instance, Karremans and Gribnau (1983) reported that the natriuretic effect of furosemide is less in elderly patients, and the change can be attributed to diminished renal excretion of the drug. The reduced renal clearance suggests dosage should be lowered in old patients; but the blunted pharmacodynamic response secondary to this "physiologic" change in pharmacokinetics counters this. Since other diuretics also act on the luminal side of the kidney tubules, actions in the elderly should be similar (Van-Brummelen et al., 1979).

In conclusion, to the best of our knowledge, we find no previous report in Nigeria that there is no significant difference in Clcr between normotensives and mild to moderate hypertensives during treatment with these diuretics. The study also indicates that the two drugs are safe in the treatment of this category of Nigerian hypertensives with normal renal function during short-term

monotherapy.

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