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Renal excretion of fluid, electrolytes and hydrogen ions before and during diamox administration in healthy Nigerians

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Summary

Twenty-four urine specimens of eleven healthy Nigerians taken during the cool rainy season, were examined before and during diamox (acetazolamide) administration. Mean control volume-output was 1·4 litres containing 109·5 mEq Na^+, 46·6 mEq K^+ and 120 mEq Cl^- ions. Total renal acid excretion was 36·82 partitioned as 14·72 mEq titratable buffer-acid and 22·1 mEq ammonia.

During diamox intake, volume-output increased to 2·56 litres with Na^+ and K^+ contents of 222·4 and 107 mEq respectively, whilst Cl^- ions, fell to 2·6 mEq. Daily renal acid excretion was reduced by 25% and titratable buffer acid was absent in most samples but ammonia excretion showed a wide scatter with a range of 6·5–60·8 mEq.

The probable explanations for the lower potassium and total acid excretions during the control period as well as the pattern of ammonia excretion during diamox therapy are discussed.

The pattern of fluid and electrolyte excretion of man in the tropics of necessity differs from that in temperate environs, one major difference being greatly increased losses of fluid and electrolyte due to increased sweat rate. Even in the absence of overt sweating, at ambient temperatures lower than 30°C or 86°F, insensible fluid losses via pulmonary and cutaneous channels may account for as much as 1·7 l in the tropics as compared to 1 l in temperate zones (Tinckler, 1966; Elebute, 1969). However no electrolytes are lost with insensible perspiration which is a physical process, essentially beyond physiologic control and governed mainly by changes in ambient temperature and relative humidity.

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The kidney as the chief custodian of the constancy of the milleur interne, ensures that the volume and composition of urine normally represent what needs to be extracted from this internal environment to keep its composition constant irrespective of obligatory extra-renal losses. Therefore the characteristics of normal urine vary with dietary habit and external environmental factors such as temperature and relative humidity. Yet in tropical clinical practice, fluid and electrolyte therapy is usually based on figures obtained in temperate environments. Awareness of the attendant dangers associated with this practice has led a few workers in this environment to try and fill the gap.

This present study was carried out in Lagos, which for most part of the year is hot and humid. In order to minimize the effect of climate-induced sweating, this investigation was carried out during the coolest part of the year, in the months of June–September when ambient temperature ranged between 70 and 84°F and the relative humidity was between 80 and 95%. This paper is therefore designed to examine renal handling of fluid, electrolytes and hydrogen ions under these environmental conditions and to evaluate the effects of administration of acetazolamide, a carbonic anhydrase inhibitor, on the characteristics of normal urine.

Materials and methods

Eleven healthy Nigerian male subjects aged between 20 and 40 years were investigated. Eight of these were medical students (age ranged 20–24 years), whilst the remainder were members of the Department of

Physiology including the author. Each subject provided 24 h specimens of urine on at least six different occasions throughout the investigation. None of the subjects suffered from any form of urinary infection and only samples that contained neither glucose, albumin nor casts were included in this survey. No restriction was placed on fluid intake or diet, but alcohol was not allowed during any 24 h period of urine collection. Each subject completely emptied his bladder at 0700 on the morning of each urine collection period and this sample was discarded. All samples passed subsequently were collected in large brown Winchester bottles (containing 3 ml of toluene as preservative) until 0700 the following day when the bladder was again completely emptied, this time into the collection bottle. Every subject provided three 24 h specimens during the control period, and after a break of 7 days, the same procedure was repeated, except that in addition each subject was made to take 250 mg acetazolamide (one tablet of diamox) at 0800, 1400 and 2000 respectively on each day for another 3 days of urine collection. The medical students who constituted 75% of the subjects, being on institutional diet, virtually had the same items of food before and during diamox intake.

All 24 h urine specimens were analysed immediately at the end of each urine collection period. Volumes and specific gravities were accurately measured with glass measuring cylinders and simple hydrometers. The pH was determined with a model 23A direct reading pH meter whilst urinary sodium and potassium concentrations were estimated with an EEL flame photometer. Urinary chloride was estimated as for plasma chloride by the modified method of Schales & Schales (1941).* Titratable acidity was obtained by titrating 20 ml aliquot of urine against 0·1 N NaOH using 1 ml phenol-red as indicator (modified from Henderson & Palmer, 1914).* Ammonia excretions were estimated by the Conway microdiffusion technique using the Conway unit (Conway, 1950b; Conway, 1957a).*

The value of each urinary constituent was calculated in mEq/l and then converted into total 24 h excretion by multiplying by the appropriate 24 h urine volume.

Results

Each subject's average 24 h renal excretion of the various ions over the 3 day period before and during diamox intake are plotted in the scattergram in Fig. 1. Table 1 is a grand summary of the mean, standard deviation (s.d.) and range of each 24 h urinary constituent for all the subjects (thirty-three specimens in each series) also before and during diamox administration. During the control period (i.e. before diamox intake), the mean 24 h urine volume was 1·4 l with a specific gravity of 1010. Total daily renal excretions of sodium, potassium and chloride ions were 109·5, 46·6 and 120 mEq respectively. The mean daily urinary pH was 6·46 with a range of 5·8–7·4. Total 24 h renal excretion of hydrogen ions came to 36·82 mEq, partitioned as 14·72 mEq of titratable buffer acid and 22·1 mEq of ammonia.

During the 3 day period of diamox administration, the mean 24 h urine volume was 2·56 l which is almost double the control value while the specific gravity fell to 1007. There were considerable alterations in electrolyte contents of urine. Daily sodium and potassium excretions rose to 222·4 and 107 mEq respectively whilst chloride ions virtually disappeared from the urine, the mean daily excretion falling to as low as 2·6 mEq (Table 1, Fig. 1). Twenty-nine out of the thirty-three specimens of urine were on the alkaline side of blood pH, the mean value being 7·89 with a range of 7·35–8·37 pH units. Only four urine specimens with pH lower than 7·4 had any titratable acid component and the highest daily excretion of this acid in these specimens was 4·97 mEq. The pattern of ammonia excretion showed a remarkable change, rising from a control daily output of 22·1–27·8 mEq during diamox intake. There was also a wide scatter in the amounts excreted by the individual subjects (Table 2, Fig. 2). The overall effect of this was that total 24 h hydrogen ion excretion fell from 36·82 mEq at control period to 28·14 mEq during diamox intake, a percentage reduction of approximately 25%.

Discussion

The months of June–September when this study was carried out fall within the heavy rainy season of the southern belts of Nigeria. During this season, the weather is generally cool and humid so that extrarenal fluid and electrolyte losses are reduced to minimal levels. Thus in the control period, our subjects' mean 24 h urine output of 1·4 l containing 109 and 120 mEq of sodium and chloride ions respectively does not differ much from figures quoted

* All analytical methods used above are obtained and corresponding references quoted from Varley (1967).

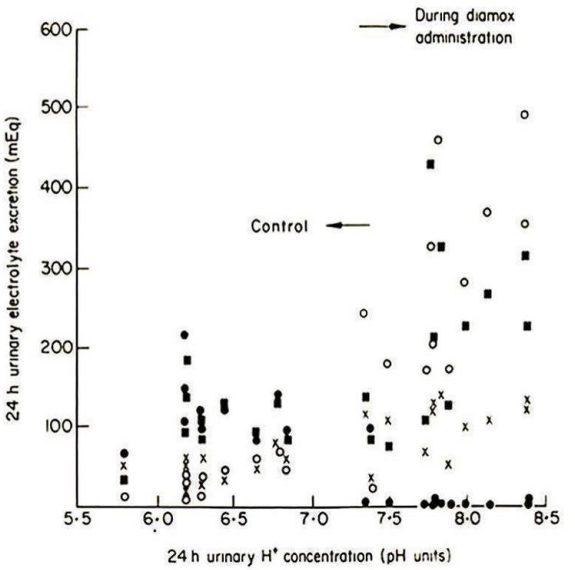

FIG. 1. Scattergram of electrolyte excretion in thirty-three 24-h urine specimens of eleven healthy Nigerians before and during diamox administration. Note HCO_3^- are approximate estimated values only and are therefore excluded from the text. ×, K^+; ■, Na^+; ○, HCO_3^-; ●, Cl^-.

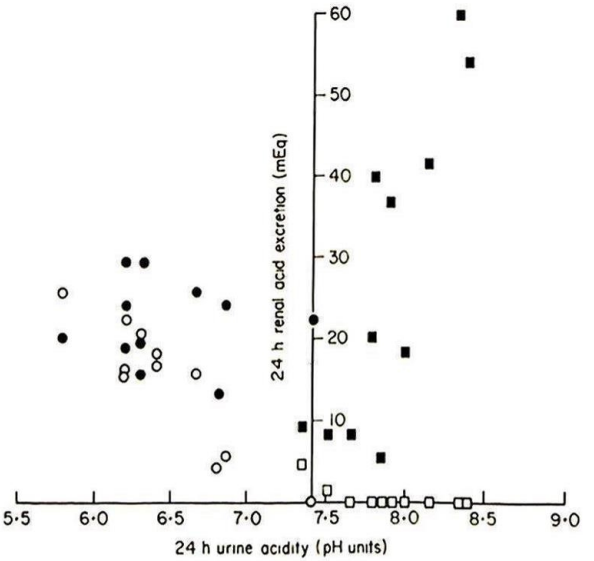

FIG. 2. Shows the relationship between urinary pH and excretion of titratable buffer acid and ammonia in the subjects, also before and during diamox administration (○, titratable acid; ●, ammonia; before diamox intake) (□, titratable acid; ■, ammonia, during diamox intake).

TABLE 1. Summary of 24 h urine data in eleven healthy Nigerians

24 h urine specimens (thirty-three in each series)	Control			During diamox administration		
	Mean	s.d.	Range	Mean	s.d.	Range
Volume (litres)	1·40	±0·37	0·83–2·26	2·56	±1·19	1·29–4·86
Specific gravity	1010	±5·12	1001–1020	1007	±2·82	1003–1012
Total Na^+ (mEq)	109·5	±42·3	37·4–161·0	222·4	±111·8	107·2–426·7
Total K^+ (mEq)	46·6	±15·3	19·95–76·2	107·2	±27·32	51·3–138
Total Cl^- (mEq)	120·0	±36·6	62·7–216	2·6	±1·07	1·2–4·82
Urine pH	6·46	±0·42	5·8–7·4	7·89	±0·31	7·35–8·37
Total titratable acid (mEq)	14·72	±6·62	0–25·73	0·26	±1·49	0–4·97
Total ammonia (mEq)	22·1	4·96	13·2±29·4	27·8	±19·8	6·5±60·8
Total acid excretion (mEq)	36·82	10·47	17·6–50·1	28·14	±19·2	8·4±60·75

TABLE 2. Individual mean 24 h urine volume, pH and NH_3 values before and during diamox administration

Subjects	Control			Diamox		
	Volume (litres)	pH units	NH_3 (mEq)	Volume (litres)	pH units	NH_3 (mEq)
1	0·830	5·8	20·1	1·592	7·35	9·3
2	0·930	6·2	18·2	1·290	7·50	8·4
3	1·340	6·2	23·5	1·470	7·65	8·5
4	2·260	6·2	29·0	2·580	7·80	20·6
5	1·283	6·3	19·7	4·471	7·80	40·3
6	1·357	6·3	29·4	2·590	7·85	6·5
7	1·620	6·4	18·4	2·193	7·90	36·2
8	1·832	6·7	25·0	1·465	8·00	18·2
9	0·896	6·8	13·2	2·731	8·20	42·1
10	1·648	6·85	24·0	2·915	8·35	60·8
11	1·640	7·4	22·6	4·860	8·37	54·3

for temperate environs (Pitts, 1968). However the daily potassium excretion of 46·6 mEq in our subjects is comparatively low, and this is probably a reflection of their lower dietary intake of fresh fruits and vegetables. (These dietary items are very expensive in the city of Lagos, where the bulk of the food requirements of its inhabitants is brought from the hinterlands, for economic reasons fresh fruits and vegetables are given the lowest priority.)

Badoe & Osafo (1971) in neighbouring Ghana reported in the subjects studied by them a mean daily urinary output of 1·44 l with a total sodium and potassium excretion of 114 and 47 mEq respectively. From the ambient temperature range of 65–86°F during their study, it may be inferred that their investigation was also carried out during the rainy season. Lagos and Accra, capitals of Nigeria and Ghana respectively lie on the same latitude, 6°N of the Equator, with Accra 0° and Lagos 3°E of the Meridian of Greenwich. These two capital cities are most likely subjected to the same dietary restrictions, thus establishing a common basis for the relatively low potassium excretion in the two groups of subjects studied.

The mean daily urine pH of 6·46 in our subjects during the control period is slightly more alkaline than the average pH of 6 quoted in most textbooks of physiology, and the total daily renal acid excretion of 36·8 mEq is also on the low side of 'normal'. 'A healthy individual on a mixed diet excretes through the kidneys 40–80 mEq of non-volatile acid as titratable buffer acid and ammonium salts' (Pitts,

1968). This acid is derived from the metabolism of protein-rich foods which yield high acid residues. However the typical Nigerian diet is essentially bulky carbohydrate food with little supplement of meat and fish proteins. In the developed countries, the daily intake of protein per capita was estimated to be 90·6 g of which animal protein constituted 48·9 g; comparable figures for developing countries were 56·4 and 11·4 g respectively (F.A.O. Report, 1970). Therefore the lower intake of protein particularly of animal origin seems the most plausible explanation for the lower renal acid excretion in our subjects.

The kidneys play a major role in the regulation of normal acid-base balance of body fluids mainly by secreting hydrogen ions into urine. It is this tubular secretion of hydrogen ions in exchange for sodium ions in luminal fluid that is the key mechanism underlying the reabsorption of bicarbonate, the generation of titratable buffer acid and the excretion of ammonium salts. The cells of proximal and distal convoluted tubules contain the enzyme carbonic-anhydrase (Pollak *et al.*, 1965). This enzyme greatly accelerates the reaction between carbon dioxide and water to form carbonic acid, the ionization of which provides hydrogen ions secreted into tubular lumen. The administration of acetazolamide, a potent inhibitor of carbonic anhydrase (Pitts, 1968) to our subjects may be expected to considerably reduce the formation of hydrogen ion within the tubular cell and therefore its availability to the luminal exchange system.

In most mammals, acetazolamide lowers H^+ and NH_4^+ excretion producing the general pattern of increased renal excretion of HCO_3^-, Na^+, K^+ and osmotically obligated H_2O (Maren, 1967). In consonance with the general effects of acetazolamide in mammals, the volume output of our subjects during the administration of this drug almost doubled, while sodium and potassium ion excretion increased considerably and the mean urine pH rose to 7·89 units. Also the negligible excretion of chloride ions in our subjects agrees with the observation of Weinstein (1968) that in acetazolamide infused rats, the final urine was virtually chloride-free and that proximal and distal tubular cells remained capable of absorbing sodium with chloride.

The titratable buffer acid excretion during acetazolamide administration was virtually zero though ammonia excretion showed a wide scatter from individual to individual ranging from 6·5 to 60·8 mEq per day (Table 2, Fig. 2). Consequently the total daily renal acid excretion fell only by 25% from control levels. During carbonic anhydrase inhibition, hydrogen ions secreted into the lumen in exchange for sodium, would combine with HCO_3^- left behind to form carbonic acid, which in the absence of luminal brush-border carbonic anhydrase would not dehydrate as rapidly as before. Its accumulation in the tubular lumen would thereby lower the pH in this segment of the nephron. This is the mechanism claimed to be responsible for the generation of a disequilibrium pH observed by Rector *et al.* (1960), in the proximal tubular lumen of rats infused with acetazolamide. Since the diffusion of free base (NH_3) is in the direction of a high hydrogen ion concentration (Pitts, 1968) then ammonia may be expected to diffuse rapidly from tubular cells into proximal tubular lumen, where it will be trapped as non-diffusible ammonium ions. It is our belief that most of the ammonium salt excreted in our subjects during diamox administration was formed in this way. It is pertinent to note at this juncture that Hayes, Owen & Robinson (1966) observed that acetazolamide administration did not decrease proximal ammonia secretion in the rat.

Another possible contributing factor to the high ammonia excretion in our subjects may be the high rate of urine flow during diamox administration. Pitts (1968) declared that when urine pH is low, the gradient of free base is high and rate of diffusion little affected by urine flow. If the pH of the urine is only slightly below that of blood, the rate of diffusion becomes dependent on urine flow. The higher the flow rate, the greater is the diffusion of the free base, merely because the free base is continually removed in the urine and fresh filtrate is supplied into which further diffusion can occur. Thus in our subjects, the higher urine flow rate in the distal convoluted tubules consequent on unabsorbed bicarbonate may compensate for the expected slow rate of diffusion of NH_3 usually associated with alkalinization of tubular fluid. It would therefore appear that despite considerable alkalinization of urine, during diamox administration, the kidneys may still excrete large amounts of ammonium salts. Figure 3 illustrates an attempt to correlate 24 h urinary pH with volume output and total ammonia content. It will be seen that below the pH of blood, total 24 h ammonia output was in the range of 10–30 mEq despite urine flow rates of less than 2 l; whereas at about the pH of 8, total ammonia excretion rose correspondingly with volume output.

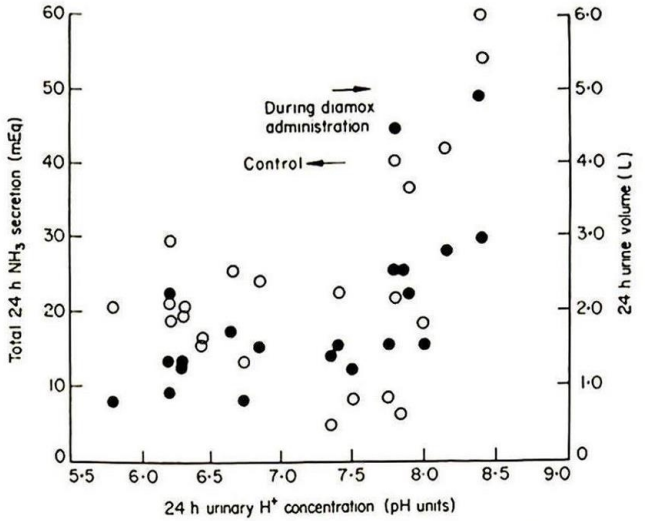

FIG. 3. Is an attempt to illustrate some relationship between urine flow rate and ammonia excretion particularly at high urinary pH values. ○, NH_3; ●, urine volume.

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