

MMED DISSERTATION

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**A PILOT STUDY ON
ELECTROLYTE AND WATER LOSSES IN PATIENTS WITH AIDS-RELATED
PERSISTENT DIARRHOEA AND MALNUTRITION AT UNIVERSITY
TEACHING HOSPITAL, LUSAKA.**

BY

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A Dissertation submitted to the University of Zambia in partial fulfillment of the requirement for the degree of Master of Medicine in Internal Medicine.

(School of Medicine)
**THE UNIVERSITY OF ZAMBIA
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DECLARATION

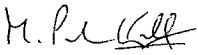
I declare that this dissertation represents my own work and that it has not previously been submitted for a degree, diploma or other qualification at this or another University.

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ABSTRACT

Chronic diarrhea results in salt and water loss resulting in blood volume depletion which may lead to hypovolaemia, postural hypotension and deterioration in quality of life. These may be compounded by metabolic derangements and malnutrition so that these patients suffer from a persistent diarrhea-malnutrition syndrome.

We carried out a pilot study at the University Teaching hospital, Lusaka, in order to analyze the severity of metabolic deficits in relation to salt and water losses in AIDS related persistent diarrhoea. 12 patients completed a full evaluation and monitoring after 3 litres of normal saline fluid challenge daily over a 3 day period. A clinical examination was done and Karnofsky score noted on day one. In addition a spot urine sample and a blood sample were collected at 09:00 hours, before fluid challenge, for measurement of baseline values for urine sodium and for serum sodium, potassium, glucose, creatinine and aldosterone.

The urine and blood collection was repeated every day for the next three days after the 24 hour fluid challenge to monitor the subject's response. The subjects had an electrocardiogram done on day one to detect any heart abnormalities which may contraindicate participation in the study. On day four, a second and final Karnofsky score was noted to observe for any improvements in the subjects.

This pilot study was able to show that in persistent diarrhea patients have severe salt and water deficits and that the 3 litres daily fluid challenge was not enough to fully restore blood volume. It was also shown that half of the subjects had adrenal cortical failure which made homeostasis of electrolytes difficult to restore. All subjects examined were in a hypoglycaemic state but only one renal failure.

Although the subjects had evidence of Na^+ and water depletion, there was no evidence of postural hypotension. Overall the study was able to show that infusion with normal saline improved the blood pressure, the quality of life and well being of the subjects over three days. However the amount of 3 litres of fluids was not adequate to restore serum electrolytes and effective plasma osmolarity.

This dissertation is dedicated to my family

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CHAPTER 1

1.0 BACKGROUND INFORMATION

In 2001, during the course of investigations into gut permeability as part of another study, it was noted that HIV-seropositive patients with diarrhoea had low urine output (Zulu and Njovu unpublished observations). Furthermore, the amount of oral, and later intravenous, fluid required to restore urine output was surprisingly high. As many of these patients were just about to be discharged from The University Teaching Hospital (UTH), it was postulated that there might be a salt and water deficit in these patients, which may require more aggressive treatment in order to restore quality of life during hospital treatment.

It is well known that patients with diarrhoea develop salt and water depletion, and treatment with oral rehydration therapy has saved many lives throughout the world. However, patients with persistent diarrhoea have much more complicated metabolic derangements, including a degree of malnutrition so that the clinical syndrome is appropriately termed the persistent diarrhoea-malnutrition syndrome (PDM).

Due to resource constraints, detailed analysis of the severity of the metabolic deficits in these patients in Lusaka has not been carried out. By analogy with children with PDM, it is likely that they have depletion of potassium, phosphate and magnesium, together with other micronutrients. Furthermore, the same constraints mean that these patients are managed with modest amounts of oral rehydration therapy, and few guides are available as to how much should be administered.

The chronic wasting of fat, non-fat body mass (1), complicates the situation, and therefore interpretation of isolated measurements of renal function may be difficult. Patients with advanced AIDS are also at risk of adreno-cortical impairment, renal parenchymal disease, and autonomic failure so that there may be several factors which contribute to disorders of salt and water handling and their effect on blood pressure and general well-being.

It is likely that in patients with AIDS-related PDM, simple salt and water depletion as a consequence of diarrhoea will be the dominant factor explaining volume depletion and postural hypotension. However, in individual cases it will be necessary to assess whether renal or hormonal disorders are likely to influence the interpretation of results.

1.1 STATEMENT OF THE PROBLEM

Persistent diarrhoea is one of the most common reasons for admission to the medical wards at UTH in HIV/AIDS patients. A great proportion of the diarrhoea in Zambia is due to protozoa infection with a few patients having no organism isolated in the stool. The major consequence of persistent chronic diarrhoea is massive fluid loss over time, electrolyte and micronutrient loss. Fluid replacement therapy in the form of intravenous fluids or oral rehydration salts is used to resuscitate these patients at UTH. However, the actual fluid needs for such patients are not known in Zambian patients. Often clinical assessment is used to determine adequacy of rehydration. This may have contributed to the increased mortality in such patients due to dehydration resulting from inadequate fluid replacement. UTH has few guidelines on how much fluids should be given to persistent chronic diarrhoea patients and furthermore indices for use in assessment of dehydration and rehydration in such patients are not readily available. Knowledge on adequate fluid replacement in these patients would go a long way in improving the quality life of many HIV-infected persons with persistent chronic Diarrhoea.

1.2 STUDY JUSTIFICATION

This study will try to determine the adequate amounts of fluids required to fully replenish the fluid and electrolytes lost over time. This study will determine whether adequate rehydration will improve the patient's quality of life and well-being. Data will help reduce or estimate the duration of hospital stay for patients following adequate rehydration, this will also help in creating space required for other clinical problems and costing for the hospital needs. Based on mineral deficit, it will be possible to draw guidelines on the most appropriate fluids to use on such patients.

1.3 HYPOTHESIS

1. HIV-infected patients with persistent chronic diarrhoea malnutrition syndrome lose electrolytes and water which is not being adequately replaced in the UTH medical wards.
2. Hormonal deficiencies may complicate management.

1.4 RESEARCH QUESTIONS

1. What is the salt and water deficit of HIV-infected patients with persistent chronic diarrhoea-malnutrition syndrome?
2. What is the approximate total intravenous fluid requirement to resuscitate these patients?
3. Does adequate hydration with normal saline improve the quality of life and blood pressure of PDM patients?
4. Is there any evidence of adrenal cortical failure in PDM patients?
5. How long does it take for the patients to stay in hospital following adequate rehydration?
6. What complications does fluid challenge cause in these patients?

1.5 GENERAL OBJECTIVE

Using a simple fluid challenge of normal saline, It is proposed to estimate the severity of the electrolyte and water deficit in these patients, together with an assessment of the hormonal responses to such a deficit. It will be assessed whether fluid challenge would improve blood pressure, general well-being and quality of life.

1.6 SPECIFIC OBJECTIVES

1. To measure urine sodium and potassium output before and after a challenge of intravenous fluid in convalescent patients with AIDS-related PDM. Each patient will act as his/her own control.
2. To measure aldosterone activity in early morning blood samples before and after the challenge.
3. To measure the general well-being (such as Karnofsky score) before and after fluid challenge.
4. To determine the amounts of electrolyte and water deficits in chronic diarrhoea patients.
5. To determine the adequate amounts of rehydration fluids needed by chronic diarrhoea patients.

CHAPTER 2

2.0 LITERATURE REVIEW

2.1.0 AETIOLOGY

The diarrhoea wasting syndrome afflicts many AIDS patients at some point in their illness (2,3). This syndrome often associated with significant malabsorption, may adversely affect nutritional status, immune function, and shorten survival of patients infected with HIV (2-5). The main organisms which cause chronic diarrhoea in AIDS patients are; *Cryptosporidium parvum*, *Isospora belli*, *Cyclospora cayetanensis* (coccidian – oocyst forming), microsporidia (*Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*) (spore forming) (6,7,8,9). These organisms have also been implicated as important pathogens in otherwise health individuals. In UTH, the commonest organisms causing diarrhoea are *Isospora belli*, microsporidia and *Cryptosporidium parvum*. The incidence of *C. parvum* is particularly high during the rainy season (10). Although persistent chronic diarrhoea and wasting is the subject of this study, literature has been reviewed to present a complete picture of PDM from aetiology, pathogenesis, clinical features to treatment of such AIDS patients.

2.1.1 LIFE CYCLE OF PARASITES

Infection by the spore forming protozoa is by direct contact with another human or through food or water contaminated by another human(11, 12) . Ingestion of the spore (microsporidia) or oocyst (Coccidia) begins a life cycle for the protozoa. The ingested spores release sporozoites, which invade primarily small intestinal enterocytes progressing through two stages. The merogonic (or schizogonic) and the sporogonic (or gametogonic) stages. The merogonic stages involves the maturation and development of meronts to reproduce and multiply in the infected cell or to infect other enterocytes of the host. This asexual stage allows the infection to spread to many enterocytes even if the host is not repeatedly exposed to the organism. The sporogonic stage involves the maturation and

development of sporozoites enclosed in oocyst or spores. As the infected enterocytes die, oocyst or spore shedding occurs. The oocyst or spores are sloughed into the gut lumen to be excreted in the stool. Invasion below the epithelial surface is uncommon (13). Adherence and invasion of enterocytes results in release of inflammatory mediators which induces the secretion of Na⁺, Cl⁻ and water.

2.1.2 EPIDEMIOLOGY

The epidemiology of the spore forming protozoa is not fully understood because of lack of complete surveillance, wide spread serologic surveys and extensive stool examinations by trained observers using sensitive techniques. In general the infections are more common in developing countries linked with poor environmental sanitation, overcrowding and poverty. Worldwide the predominant method of transmission is faecal-oral route. Transmission can be direct or can occur through contaminated water and food (14,15,16,17). Cryptosporidia cause substantial illness throughout the world. The prevalence of the organism in stool varies according to the characteristics, symptom status and immunologic function of the population studied. The prevalence of cryptosporidium in stool is 1 to 3 % in Europe and North America (18,19) , 5 to 10 % in Asia and Africa (18,19). However, positive serology for cryptosporidia in developed countries is between 32 to 59 % in adults (20). Cryptosporidia are highly transmissible in a family setting. Cryptosporida have been implicated as a cause of diarrhoea in travellers (21,22) and epidemic diarrhoea in hospitals (23), day care facilities (24) and community centres (17, 25) and Institutions (18,26).

Isospora belli is less common than *C. parvum*. It is endemic in many parts of Africa, Asia, and South America. Exact prevalence rates and details of epidemiology are not known but in HIV seropositive patients it ranges between 8-32 % (27). Different frequencies of infection in patients with AIDS often reflect the different prevalences of pathogens in different environments.

Knowledge of epidemiology for human microsporidia is much more limited. However, the fact that microsporidiosis is a much common infection in HIV/AIDS patients and that the potential for human to human transmission of microsporidia is high, this suggests that

it might be a common worldwide intestinal pathogen for humans (14). This has been supported by a high prevalence of *Enterocytozoon bieneusi* in AIDS patients around the world.

Cyclospora has been identified worldwide in stool of both immunocompetent and immunocompromized patients with diarrhoea (28,29). A study in Peru found both cryptosporidia and cyclospora occurring at same time of the year in children aged 1 to 2 years (28).

All four intestinal protozoa are frequent AIDS-related pathogens. Cryptosporidia are found in the stools of 10 to 20 % of AIDS-associated diarrhoea (18,30,31,32,322,34,35,36,37,38). Microsporidia is more commonly associated with chronic diarrhoea in AIDS patients than cryptosporidia, with a prevalence of 6 to 50 % (14,39). The frequency with which cryptosporidia and microsporidia are identified in stools of patients with AIDS is related to the CD4 lymphocyte count of less than 100 cells/mL and the presence of gastrointestinal symptoms.

Estimates of prevalence of *Isospora belli* in AIDS-related diarrhoea in USA and Europe is 2% (37,40), 9.9% in Brazil (41), 12% in Congo DR (42), 16% in Zambia (43) and 12% in Haiti (44). The prevalence of *Cyclospora cayetanensis* in AIDS patients is 11 % (44).

The prevalences above may be underestimates. This may be caused by untrained observers confusing cyclospora with cryptosporidia; acid-fast stain not always done on stool specimens, and frequent use of trimethoprim-sulfamethoxazole prophylaxis which may make diagnosis harder.

2.2 PATHOGENESIS

Infections by all four intestinal spore-forming protozoa has been associated with substantial alterations in intestinal structure and function, but the pathogenesis of the predominant symptom, diarrhoea, is not completely understood. The hypothesized sequence of events is as follows: After the initial invasion of the enterocytes by spore forming protozoa, the epithelial cells release cytokines (i.e. Interleukin-8) that activates resident phagocytes and recruit new phagocytes into the lamina propria from the blood (45). These activated leukocytes release soluble mediators of inflammation which

increase intestinal secretion of chloride and water and inhibit absorption (46,47). The mediators include histamine, serotonin and adenosine, which increase secretion and inhibit absorption by acting directly on the epithelial cell. Prostaglandins, leukotrienes and platelet-activating factor act on the enteric nerves to induce neurotransmitter-mediated intestinal secretion. Enterocyte death may be a direct consequence of parasite invasion, multiplication, and extrusion or inflammation mediated by T cells or proteases and oxidants secreted by the mast cells (45).

Activated T cells can affect epithelial cell growth and produce villus atrophy and crypt hyperplasia with increased leukocytes in the lamina propria (48). Invasion and ulceration do not occur. Cellular changes may include cell shape changes from columnar to cuboidal to pleomorphic. This may be accompanied by atrophy of microvilli, swelling of mitochondria, golgi apparatus and endoplasmic reticulum,; with accumulation of lysosomes and lipid vacuoles(49). In heavy microsporidial infection sloughing of strips of enterocytes, and denuding of the tips of villi occurs (49,50). This morphological abnormalities also occur in cryptosporidial, cyclosporidial and Isosporidial infections. It is this distortion of the villus which causes nutrient malabsorption and osmotic diarrhoea (51,52,53). This pathogenesis has been shown to be true for cryptosporidiosis.

Invitro studies have also shown that decreased sodium absorption is directly related to both decreased villus surface area and inhibition by prostaglandin E2 produced by inflammatory cells. It has not been shown that cryptosporidia produces cytotoxins. However, parasite density in enterocyte determines severity of cell damage and diarrhoea especially in AIDS patients who lack effective immunity to combat the parasite invasion (54). Therefore the pathogenesis of diarrhoea caused by cryptosporidia and perhaps other intestinal spore forming protozoa is due to a complex interaction between the host and parasite factors.

The intestinal intracellular protozoa are probably also responsible for much of the so called pathogen-free diarrhoea seen in HIV patients. It has been shown that microsporidia effect on the small bowel is to impair absorption of fats, carbohydrates, and micronutrients. Among the micronutrients with impaired absorption are vitamin B12, and to some extent folate and zinc.

2.3 IMMUNITY

Epidemiologic evidence for protective immunity exists for cryptosporidia and cyclosporidia infections. The existence of protective immunity is supported by the observation that most symptomatic cyclosporal and cryptosporidial infections in residents of endemic areas occur in infants and young children. However severe and even lethal infections occur in children with apparently normal immunological function. Both T cell dysfunction as in HIV infection, and antibody defects as in IgA deficiencies can predispose patients to protracted cryptosporidial infection (55,56). The infections with intestinal spore-forming protozoa occur with increased frequency and severity in the immunodeficient host. This shows that immune mechanisms are important in keeping parasite numbers low in most normal persons. Although intestinal antibodies can reduce parasite numbers, these antibodies are not able to protect patients with AIDS from heavy parasite burdens. Cell mediated immunity is necessary to prevent heavy cryptosporidial infections in humans. The more severe the immunodeficiency, the more likely the patient is to develop chronic infection. It has been shown that improved T cell counts and immune function have been associated with reduced parasite numbers in AIDS patients (57,58,59,60,61,62,63).

2.4 CLINICAL PRESENTATIONS

Most of the individuals infected by the spore-forming protozoa are asymptomatic whether the host is immunodeficient or normal. Some preliminary data suggest that asymptomatic enteric carriage of microsporidia in AIDS patients may precede wasting and diarrhea illness (64). The other spore-forming protozoa have been known to cause acute diarrhea in normal hosts especially in infants and children living in underdeveloped countries, medical personnel, travellers, and persons in Institutions (16,18,21,27, 28,65,66,67). In normal hosts, symptomatic illness caused by cryptosporidia, isospora and cyclospora is usually characterized by 3 to 25 days of diarrhea, abdominal pain, malaise and occasional nausea, vomiting and fever. Cases characterized by diarrhea lasting months to years with isosporiasis have been documented.

Persons with immunodeficiency in general are predisposed to more frequent and prolonged infections with spore-forming intestinal protozoa. Most reported cases are in AIDS patients. The clinical presentation ranges from asymptomatic infection to severe, life threatening diarrhea, dehydration and malabsorption. Studies in AIDS-related cryptosporidiosis have shown four patterns of disease mainly transient, chronic, fulminant and asymptomatic presentations (68). Transient self-limited diarrhea was more common in patients with less severe immunosuppression, but the more severe manifestations were more common in patients with low CD4 cell counts.

Extra-intestinal disease involving cryptosporidia, microsporidia and Isospora do affect the biliary tract in AIDS patients. This produces two syndromes. First, a sclerosing cholangitis-type of lesion causing progressive, irregular obstruction and dilatation of the intra and extra-hepatic bile ducts. It presents with right upper quadrant pain and an increasing alkaline phosphate levels. The second, is a acalculous cholecystitis caused by infection of the gall bladder wall in AIDS patients. This lesion is caused by cryptosporidia, microsporidia and Isosporidia. The pancreatic duct is rarely involved. Other organs which may be affected include liver, respiratory tract and kidney (69-73)

2.5 DIAGNOSIS

Diagnosis of these intracellular intestinal protozoa depends on laboratory evaluation of stool samples. The modified Ziehl Neelsen stain (acid-fast) is used routinely to visualize oocytes of cryptosporidia, cyclospora and Isospora in stool or in duodenal aspirate. The modified trichrome stain is used to examine for microsporidia. Duodenal biopsies are also used to detect and identify cryptosporidia and Isospora under light microscopy, but in tissue biopsies Cyclospora has only been identified by electron microscopy. Small bowel biopsy are more sensitive than stool examination for diagnosis of intestinal microsporidiosis (44,68,74-76) .

2.6 TREATMENT

The main stay of treatment is with antibiotics. Treatment with paromycin is not effective in AIDS-related chronic diarrhea caused by cryptosporidiosis (77). Co-trimoxazole is effective in *Isospora* infections in AIDS patients but has to be given in high dose over 10 days (78,79). Prophylaxis with trimethoprim-sulfamethoxazole, prevents recurrent disease in AIDS patients (79). A combination of pyrimethamine and metronidazole is also useful for patients allergic to sulfonamides (44). Trimethoprim-sulfamethoxazole is effective against cyclosporiasis. *Encephalitozoon Intestinalis* can be treated with albendazole (80). There is no treatment for *E. bienusi* infection, although albendazole may improve clinical status. It is important to note that treatment is associated with decreased intensity of infection and improved intestinal function and morphology. Relapse is also common even after therapy.

The other important aspect of treatment is supportive treatment such as replacement of nutrients, water and electrolytes. It seems likely that the loss of these nutrients, water and electrolytes makes a major contribution to high morbidity and mortality. This study set out to examine the extent of water and electrolyte deficits and determine whether replacement of water and electrolytes would improve the quality of life of AIDS patients with chronic AIDS-related diarrhea.

2.7 COMPLICATIONS OF PERSISTENT DIARRHOEA

The diarrhea and vomiting in AIDS patients can be so severe that death follows through dehydration. The extreme rapid loss of fluid leads to hypovolemic shock or postural hypotension in long standing cases.

Loss of mineralocorticoid activity causes sodium loss in urine resulting in hyponatremia and high urine sodium excretion. Low sodium causes a decline in cardiac output and finally shock. These complications can be prevented by salts and mineralocorticoid (aldosterone) replacement (81). Adrenal insufficiency is a known complication of AIDS but has not been documented in Africa.

2.8.0 ADRENAL INSUFFICIENCY IN AIDS PATIENTS

2.8.1 Physiology of water and electrolyte homeostasis and hypovolemia.

Maintenance of water homeostasis requires identical levels of water intake and water losses. The daily obligatory extrarenal water loss amounts to approximately 500 mL of water, water produced by oxidative metabolism is 500 mL, whereas the insensible losses being water lost from the skin and the lungs is 1000 mL. the total water lost from the body is therefore between 1.5 to 2 litres every day.

The typical water intake of humans exceeds the minimum requirements for maintaining water balance and largely determined by social and cultural influences. Thus, normal adults usually ingest approximately 1.5 to 2.5L of water per day; the corresponding urine volume is about 1 to 2L per day. However, in certain conditions such as during exercise, pyrexia, these tend to stimulate sweating and pulmonary ventilation and water losses may go up to even 5L per day. This increases the Effective plasma Osmolality (Tonicity) which stimulates thirst and vasopressin (ADH) release.

Excessive water and electrolyte losses such as is found in chronic diarrhea leads to reduced extra cellular fluid (ECF) volume. The ECF volume provides an additional control mechanism of thirst mediated by low-pressure baroreceptors located in the cardiac atria, whose discharge is transmitted to the brain via the vagus nerve. Hypovolemia also stimulates the rennin-angiotensin-aldosterone system.

The rennin is produced in the justaglomerular apparatus by the macula densa cells in the kidneys. Renin converts angiotensinogen to angiotensin I a vasoconstrictor. Angiotensin I is converted to angiotensin II (AII) by angiotensin converting enzyme (ACE). The AII stimulates secretion of aldosterone by the cortex of the adrenal glands and also is a very potent vasoconstrictor which causes an increase in peripheral resistance. This helps to increase the blood pressure. The net effect of aldosterone is to increase reabsorption of sodium from the proximal tubules thereby retention of sodium and water thus helping to restore the blood volume. Once the blood volume is restored it increases the cardiac output and this raises the blood pressure. The adrenal glands also produce catecholamine (adrenaline and noradrenaline) which are potent peripheral vasoconstrictors. Their action increases the peripheral resistance which causes an increase in the blood pressure.

When the adrenal glands are damaged either by trauma or any inflammatory process, it results in a reduction in the production and secretion of hormones which are produced by the adrenal glands such as aldosterone and cortisol. These hormones are some of the factors which help to regulate and restore blood volume and the blood pressure following a hypovolemic state (81).

2.8.1 Adrenal insufficiency

AIDS is a multi-system disorder secondary to infection with human immunodeficiency virus (HIV). It has been shown that nearly all organs are targeted by this disease. However, adrenal gland damage and the resulting adrenal insufficiency (AI) have been shown to be more relevant to the clinical presentations and complications of this disease. The estimated incidence of AI in AIDS patients is 5-8 % (96). Cytomegalovirus infection is the major cause for adrenalitis accounting for 40 – 80 % (93). The other causes of adrenal gland damage are; Opportunistic Infections (OI) accounting for 4 -12 % such as extrapulmonary tuberculosis, *pneumocystis carinii*, toxoplasmosis, and HIV associated tumour metastases such as in Kaposi sarcoma and non Hodgkin's lymphoma (95).

It has also been shown that HIV inhibits adrenal secretion by activating polyclonal B-cell which produces antibodies against adrenal cells, therefore damaging the adrenal glands resulting in AI (92). Classical AI presents with fatigue, hyperpigmentation, hypotension, hyponatremia and hyperkalemia, but these signs and symptoms are also reported frequently in AIDS patient., which makes association with AI difficult. However, the diagnosis of AI in AIDS patients should be considered in patients with following signs and symptoms: Wasting syndrome with history of OIs such as mycobacterium tuberculosis and cytomegalovirus disease. Fatigue and hyperpigmentation in chronically ill HIV infected patients. The AI could then be confirmed by a basal cortisol level lower than 275 nmol/L at 08:30hours or low aldosterone (89).

CHAPTER 3

3.0 METHODS AND CASES

A pilot study involving a convenience sample of 18 adult patients with AIDS –related persistent diarrhoea and malnutrition (PDM), of either sex, was conducted at the University Teaching Hospital medical admission wards. The study was carried out from February to November 2004.

3.1 SELECTION OF PARTICIPANTS

i) INCLUSION CRITERIA

Patients selected for the study were those who were HIV seropositive with diarrhoea of over one month duration and their age range was between 16 to 45 years.

ii) EXCLUSION CRITERIA

Patients were disqualified from the study, if in addition to the persistent diarrhoea and malnutrition, they were diagnosed with or developed the following clinical conditions during the investigative period of four days: fever, cardiac failure, pulmonary oedema, Rheumatic or Congenital heart disease, dyspnoea, urinary tract infection, haematuria, peripheral oedema or an abnormal Electrocardiogram (other than sinus tachycardia). Of the 18 patients selected 12 fully satisfied the criteria for data to be used for analysis, whose results will be presented and discussed later in this report.

3.2 COMPLICATIONS OF INTERVENTION TREATMENT

No patients required discontinuation of therapy which would have been necessitated by any evidence of pulmonary or peripheral oedema.

3.3 ETHICAL CONSIDERATIONS

The participants were required to sign an Informed Consent form as a basis for agreeing to participate in the study. Consent to the study was preceded by a detailed explanation to the patients of the purpose of the study, the procedure of fluid administration, its risks and discomforts, benefits to them, the community and science. It was fully explained to them that all results would be confidential

Participants were allowed to discontinue with the study if they felt so without necessarily losing out on the benefits of good clinical care. Four patients withdrew from the study because they did not want blood taken from them repeatedly.

3.4 STUDY PROCEDURES

The investigations for the study were conducted over a period of three days.

Once patients were identified and consent obtained, the intervention commenced either on the same day or the following day at 09:00hours.

i) **On Day One:** The selected patients who were identified as having persistent diarrhoea and malnutrition and had signed the informed consent form underwent an evaluation which involved a history taking , physical examination and an electrocardiogram (ECG) to rule out any clinical conditions that would interfere with the fluid challenge results. Anthropometric measurements of weight and height in relation to the age were taken. The temperature and respiratory rate were taken in either the sitting or lying position. The pulse was taken in deep inspiration and deep expiration in sitting position and in lying position. The blood pressure was measured in both lying and immediately in standing positions to observe any postural hypotension. The Blood pressure readings were taken at 08:00hours and 16:00hours upon selection to the study. At 09:00hours, an intravenous line was secured, 10mL of blood was drawn for baseline investigation, after which the venous line was flushed with 10 mL of normal saline. The venous blood was quickly transported to the Clinical Chemistry laboratory for measurement of serum sodium (Na), potassium (K), Creatinine, glucose and albumin. An aliquot of the serum was frozen at minus 80 degrees centigrade(-80) and sent to St Bartholomew's Hospital in London for

the measurement of aldosterone. A careful balance recording of the 3 litres fluid intake and output was instituted.

Normal saline and not ringer's lactate was used to hydrate the patients because persistent diarrhea was a principle inclusion criterion rather than vomiting. It was also assumed that such patients tend to lose more of sodium rather than potassium from their extra cellular fluid compartment.

A Karnofsky score for the patient was determined as per criteria in appendix 6. A 24 hour urine collection was instituted for the purpose of measuring sodium loss in urine.

ii) **On Day two:** A careful balance recording of all fluid intake and output was done for the overnight fluid intake. An aliquot of the 24 hour urine collection was taken for measurement of urine Na⁺ and total volume over 24 hours noted. At 09:00 hours, 20mL of blood was collected for measurement of serum Na⁺, K⁺, creatinine and glucose. A clinical examination was conducted to detect any complication with the three litre fluid challenge. Patients were infused with a further 3 litres of normal saline over a 24 hour period. Maximum and minimum pulse rate in deep respiration, blood pressure readings to the nearest 2 mmHg at 08:00, 12:00, 16:00 hours in both lying and standing positions were taken. Another 24 hour urine collection was made.

iii) **On Day three:** The routine observations and measurements for day two were repeated and any complications that the patients developed were recorded. Another 3 litres of saline infusion was carried out.

iv) **On day four:** The routine observations and measurements done over day two and day three were repeated. Patient's progresses were recorded and their Kanorfsky score was determined. The last blood sample for aldosterone was collected.

3.5 INTERVENTION TREATMENT

The protocol advised that all patients receive 3 litres daily of intravenous normal saline over the three days of monitoring as standard treatment. This was done to monitor the response of fluid challenge to the patient over the period of monitoring. Patients did not

develop any other medical conditions that might have necessitated treatment with antibiotics.

3.6 MONITORING RESPONSE

The challenge with 3 litres of normal saline was evaluated by the clinical response of the patient, and by the changes in serum electrolytes and aldosterone, as well as urine volume and sodium. In addition blood pressure and pulse in lying and standing position were measured to detect any postural hypotension. A mercury sphygmomanometer was used to measure blood pressure. Changes in patient progress were monitored by the respiratory rate in deep respiration, development of oedema or any signs of cardiac overload. Overall patient performance and response was determined by the Karnofsky score.

3.7 BIOCHEMICAL EVALUATION AND TECHNIQUES

The blood samples drawn from the patients were quickly transported to the laboratory where the serum was separated from the blood cells by centrifugation at 4000 rpm for 10 minutes. The serum was aliquoted into 1.5 mL samples in 3mL plastic capped vials and one aliquot was frozen for aldosterone measurement. Serum sodium, potassium, creatinine and glucose were determined from the remaining sera over the three days period. To ensure reliability of the laboratory techniques and results, each set of measurements was quality controlled using three controls; pathological high and low analyte sera and normal control serum. The coefficient of variation and accuracy was noted each time a set of measurements was done to ensure reliability of results. The following techniques were used to measure the analytes above:

- a) Flame photometry: used to measure electrolytes sodium and potassium.
- b) Glucose oxidase enzyme test kit: used for measurement of glucose.
- c) Jaffe's reaction test kit: used for measurement of creatinine.
- d) Immunoradiometric assay used to measure aldosterone in London at St. Bartholomew's Hospital Radioimmunoassay reference laboratory.

Except for electrolyte and aldosterone, molecular absorption spectroscopy spectrophotometer equipment (Cobas mira-s) was used to measure the analytes. The test kits used were from BIOGROUP Zambia, agent for Human-Germany Company.

3.8 DATA MANAGEMENT AND STATISTICS

The changes in blood analytes and clinical parameters during and after the fluid challenge over the three day period were determined by comparison with baseline values measured on day one of the intervention. The trends on the response to intervention were observed by line graphs, showing mean (**X**), and standard error of the mean (**SEM**). $SEM = SD / \text{square root of } n$. A SEM high and SEM low were used to observe trends of analyte changes in blood.

CHAPTER 4

4.0 RESULTS

4.1 PATIENT CHARACTERISTICS

This pilot study on electrolyte and water balance in patients with AIDS-related persistent diarrhea and malnutrition (PDM) was carried out in the medical wards of the University Teaching Hospital (UTH), Lusaka, Zambia. The data collection involving 12 adult patients (table 1 and 2), 7 females and 6 males, took 10 months. There were 18 patients who were initially recruited for the study over this period. Eight (8) of these were lost from full participation for different reasons. Four patients died before day 4 of monitoring. The other four withdrew from the study because they did not want blood taken from them so often. In all patients an electrocardiogram (ECG) was performed to try to detect any cardiac abnormalities as fluid overload or any electrolyte imbalance could be dangerous in such patients. There were no abnormal ECG changes detected. The data being discussed involves those 12 patients who completed the study for the four days of monitoring.

Clinical data for day one are presented in table 1 and table 2.

4.2 PRESENTATION OF DATA AND DATA ANALYSIS

The results of this study are shown using line and bar graphs and tables. The graphs show, mean (X), SEM high (H) and SEM low (L).

TABLE 1. NUTRITION STATUS

N = 12, SEX RATIO; F:M , 1:1

PATIENTS NO. AND SEX	WEIGHT (Kg)	HEIGHT (m)	BODY MASS INDEX (Wt/Ht ²)	AGE (YRS)
1F	20	1.60	7.8	21
5F	54	1.60	21.1	33
6F	48	1.50	21.3	25
2F	31	1.65	11.4	36
3F	43	1.65	16.0	25
4F	39	1.80	12.0	29
10F	70	1.6	27.3	27
1M	70	1.79	22.0	48
7M	62	1.76	20.0	45
3M	73	1.79	22.8	32
4M	68	1.74	22.5	31
5M	62	1.64	23.1	32

This table shows anthropometric measurements done as an indicator of nutrition status. It shows that 4 out of 12 patients (bold figures) had a BMI of less than 20, indicating malnutrition. The patients participating in the study were selected on the basis of having chronic (persistent) diarrhea; wasting syndrome was not an inclusion criterion.

TABLE 2. BASELINE VITAL OBSERVATIONS

N = 12, SEX RATIO; F:M, 1:1

PATIENT S NO. AND SEX	BP LYING SYST DIAS	BP STANDING SYST DIAS	RR PER MIN	PR (PER MIN) INSP	PR (PER MIN) EXP	TEMP 0 C
1F	70 40	70 40	26	72	74	35.0
5F	110 70	110 80	22	88	88	38.0
6F	100 30	110 40	24	88	100	36.0
2F	100 60	110 70	18	74	74	36.5
3F	90 60	100 60	20	80	80	36.0
4F	90 60	100 60	24	82	80	38.3
10F	100 60	--- ----	28	82	---	35.0
1M	90 60	--- ----	22	80	86	36.0
7M	100 70	110 70	20	68	70	36.8
3M	120 90	130 90	26	88	90	36.0
4M	100 60	110 60	26	90	96	39.0
5M	90 60	90 60	28	96	98	36.0

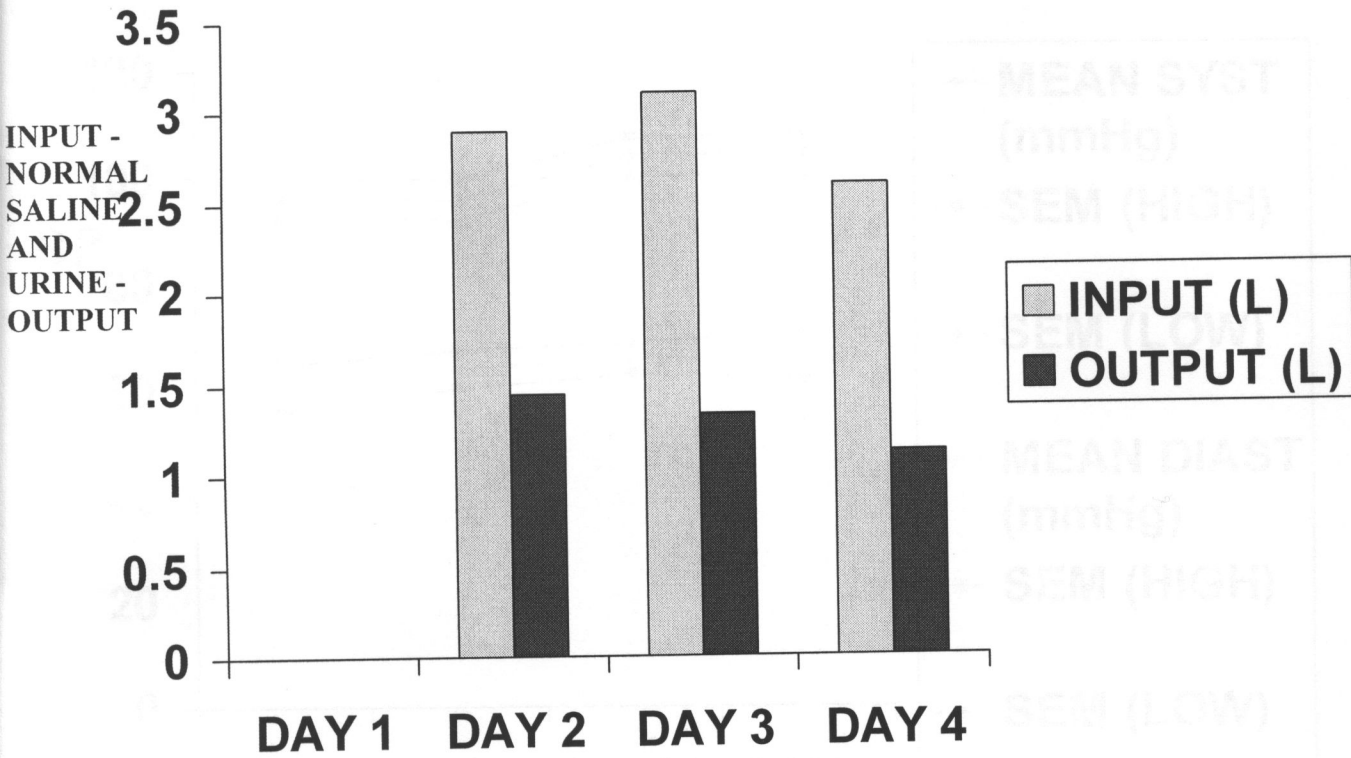
This table shows the vital observations on day one of the evaluation. It can be seen that 5 out of 12 patients had hypotension, of which none presented with a sympathetic regulatory tachycardia. This may indicate an adaptation by the body to a long standing blood volume depletion. The patients did not show any postural hypotension. BP in standing position difficult because patient was too weak to stand or breath repeatedly (10F / 1M)

TABLE 3. BASELINE CONCENTRATIONS OF SERUM, Na+, K+, GLUCOSE, CREATININE, AND CALCULATED EFFECTIVE PLASMA OSMOLARITY (EPO or TONICITY).

PATIENTS NO. SEX	Na+ mmol/L	K+ mmol/L	GLUC mmol/L	EPO mOsmol/L	CREAT umol/L	ALDOSTERONE pmol/L
1F	107	2.4	1.2	220	79	730
3F	136	2.1	2.9	277	151	628
4F	114	2.6	3.7	235	61	3035
10F	123	3.4	2.1	254	505	1821
6F	111	2.6	1.3	229	72	621
1M	143	3.1	3.9	296	71	178
3M	112	---	0.2	224	131	545
9F	----	---	2.6	----	67	<69
5F	121	5.9	2.1	256	118	<69
7F	132	2.3	8.8	277	139	<69
8F	123	2.1	5.3	256	63	<69
4M	113	2.7	0.6	232	87	<69
5M	----	---	4.0	----	134	<69

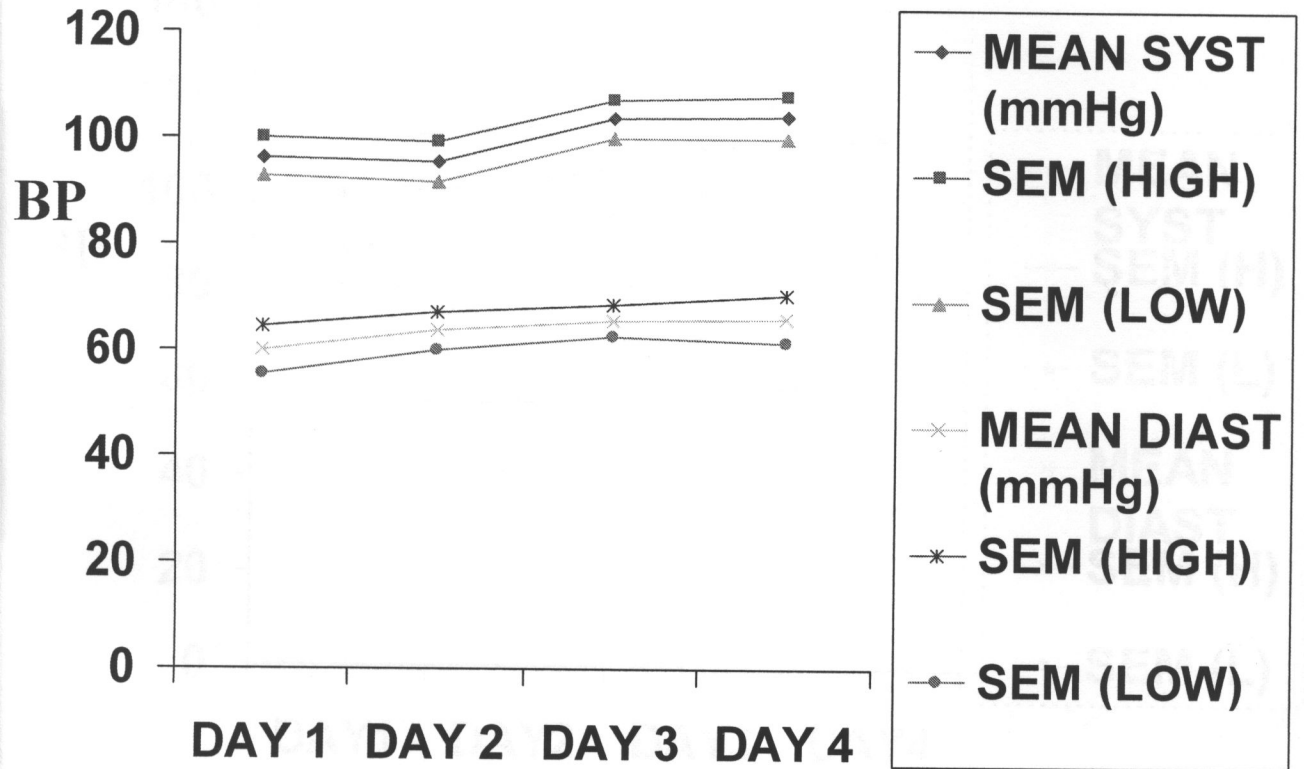
This table shows the baseline concentrations of electrolytes, glucose, creatinine, calculated EPO and aldosterone activity on day one. It shows that the majority of the patients with chronic persistent diarrhea had sodium and other electrolyte deficits which tend to lower the EPO. They were also in hypoglycemic state. About half of our patients came with adrenal failure as indicated by undetectable levels of aldosterone. One of our patients had renal failure as indicated by an abnormally high creatinine.

FIGURE 1. FLUID BALANCE AFTER 3 LITRES NORMAL SALINE FLUID CHALLENGE DAILY OVER PERIOD OF MONITORING.



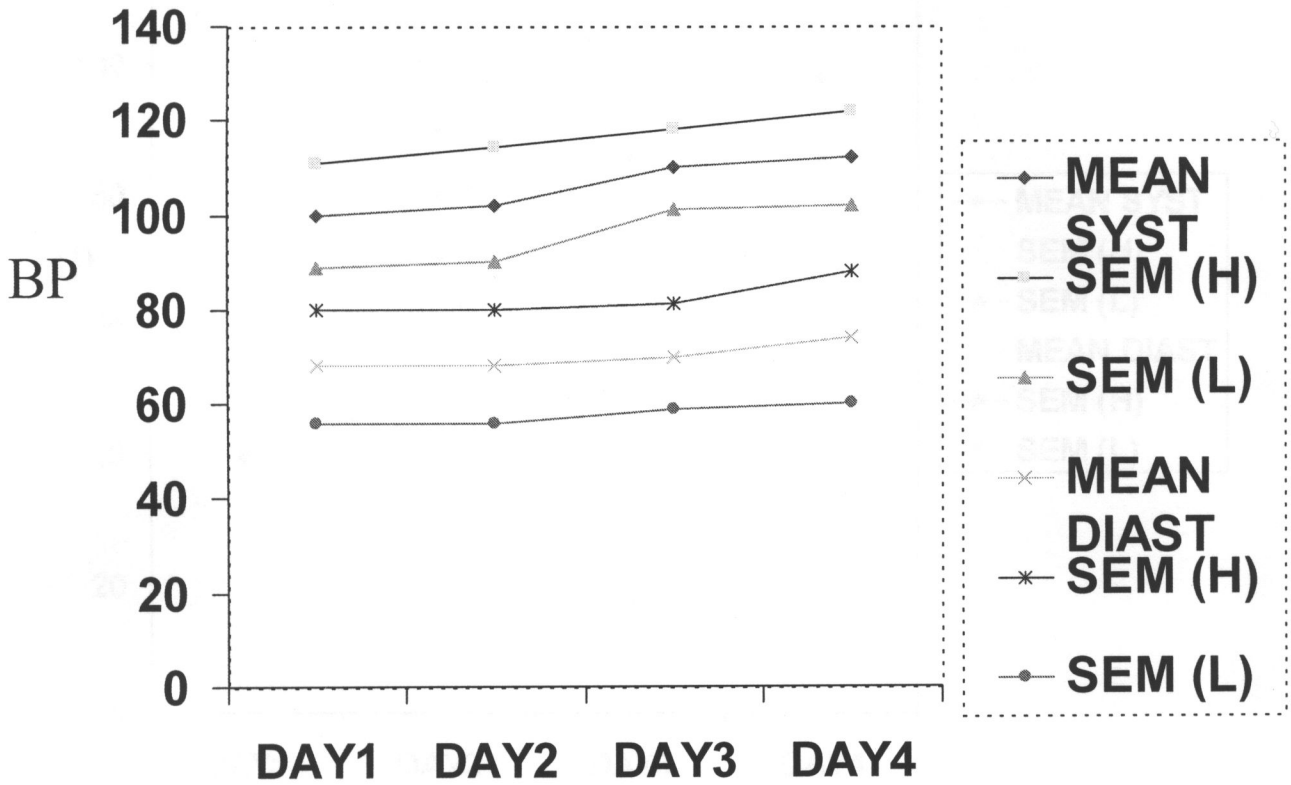
The patients showed a positive fluid balance after fluid load.

FIGURE 2. MEAN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN LYING POSITION IN BOTH SEXES.



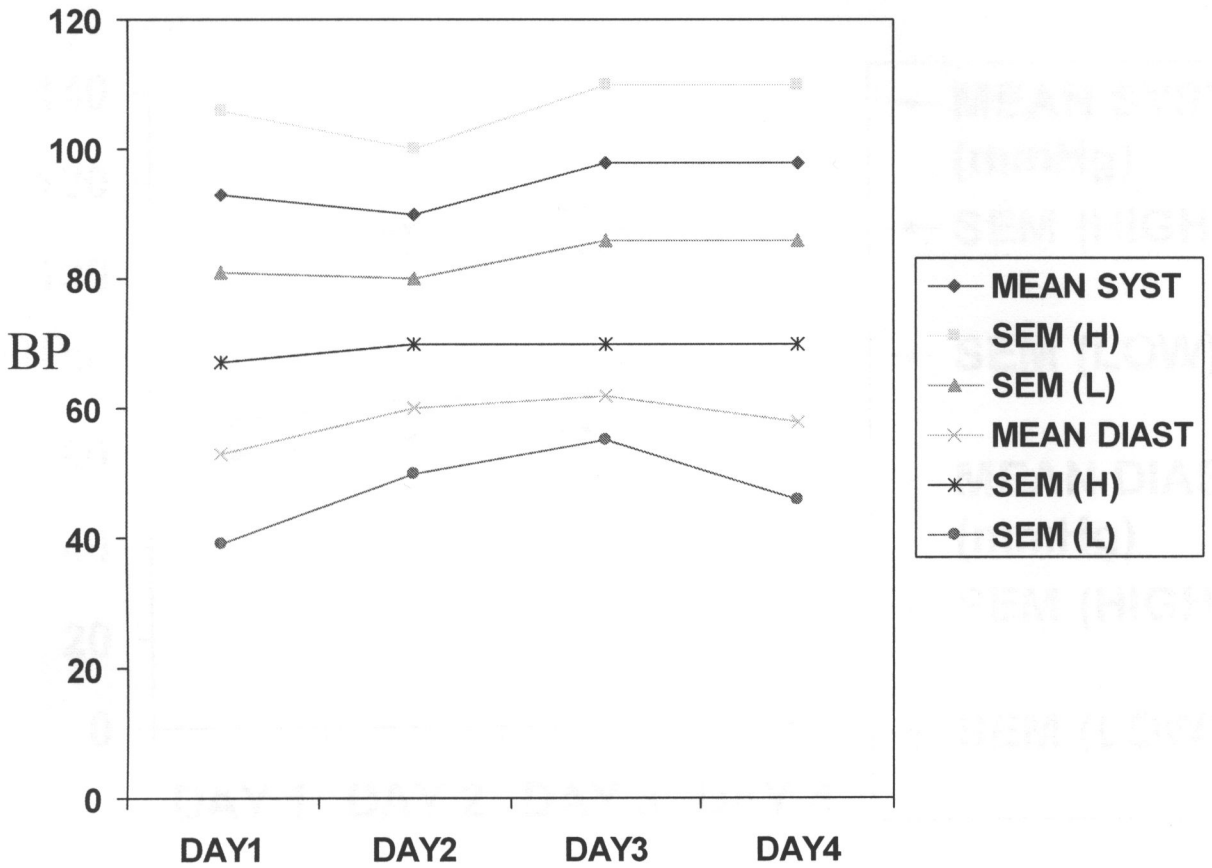
This figure shows that the systolic and diastolic blood pressure increased over time ($p=0.003$ by non-parametric test for trend).

FIGURE 3. MEAN SYSTOLIC AND DIASTOLIC PRESSURES IN LYING POSITION IN MALES



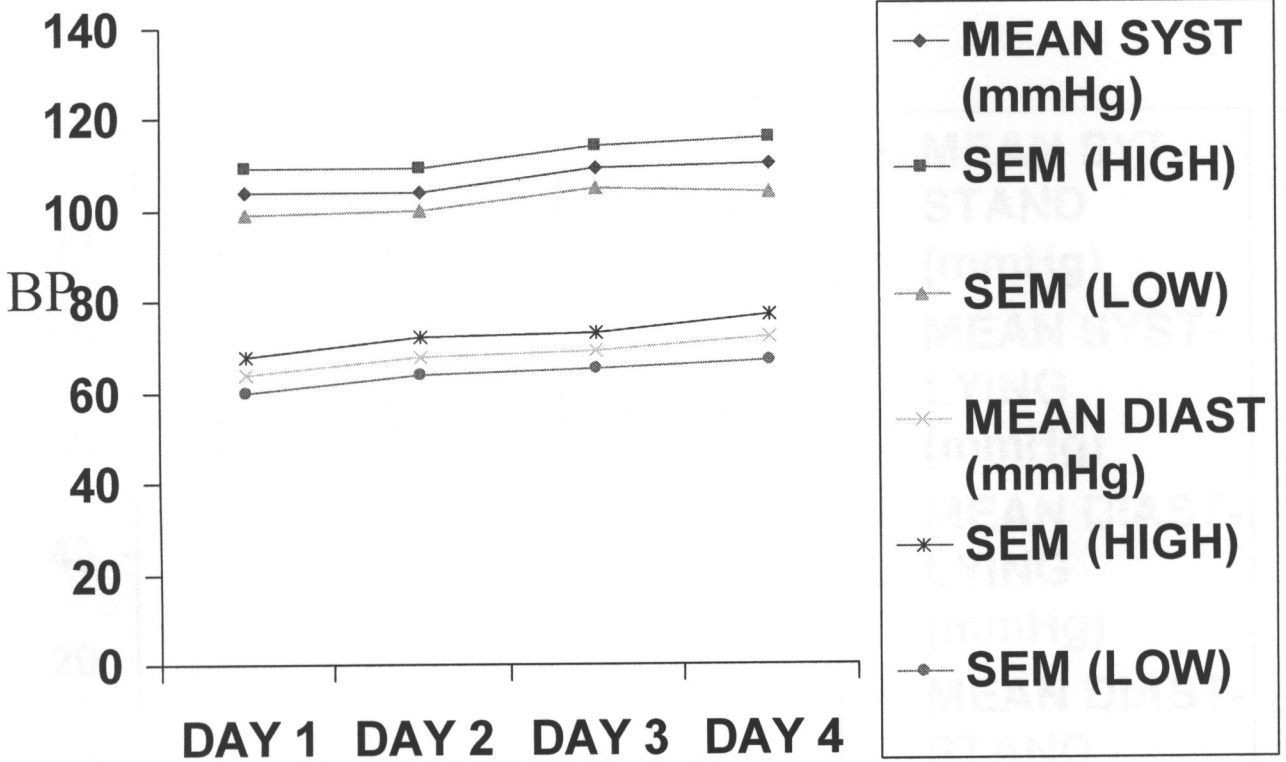
This figure shows a rise in blood pressure over time in males

FIGURE 4. MEAN SYSTOLIC AND DIASTOLIC PRESSURE IN LYING POSITION IN FEMALES



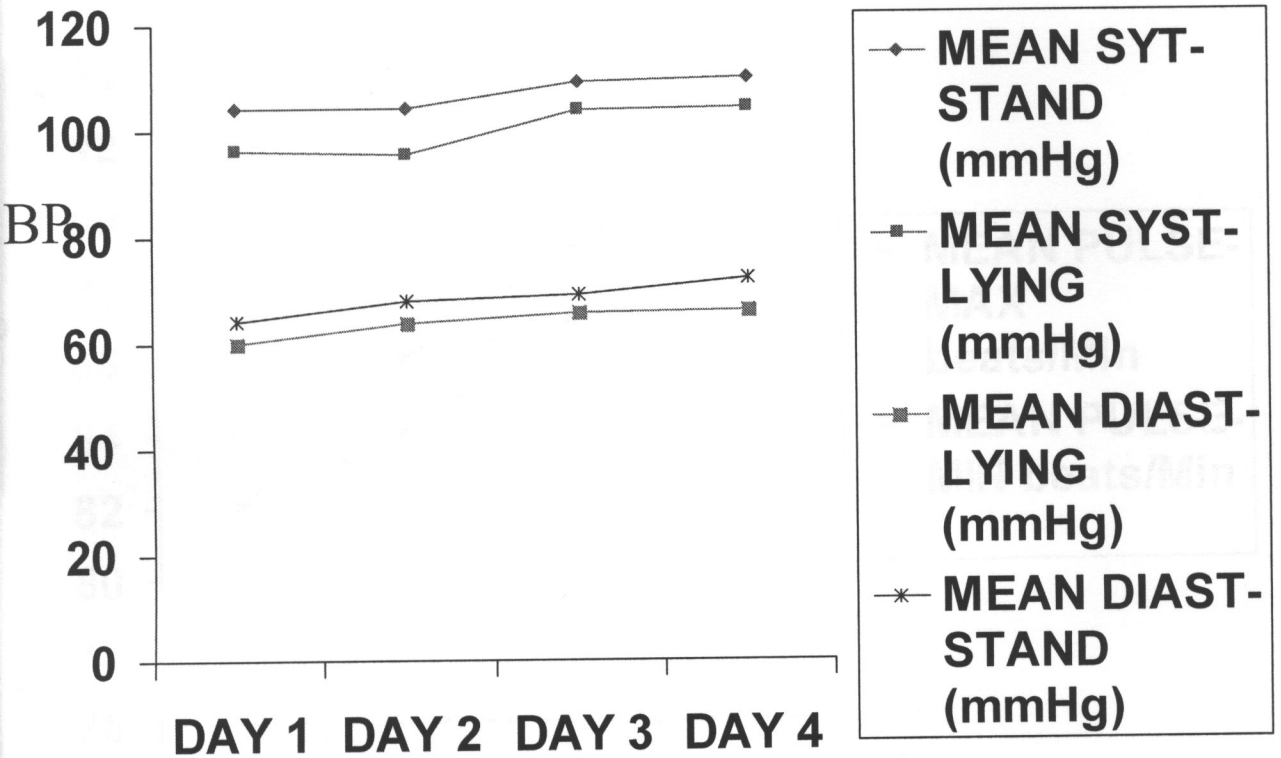
This figure shows a rise in blood pressure over time. It is clear that the systolic and diastolic blood pressure for females tended to be lower than that of males (compare with figure 3). This is consistent with normal clinical observation.

FIGURE 5. SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN STANDING POSITION.



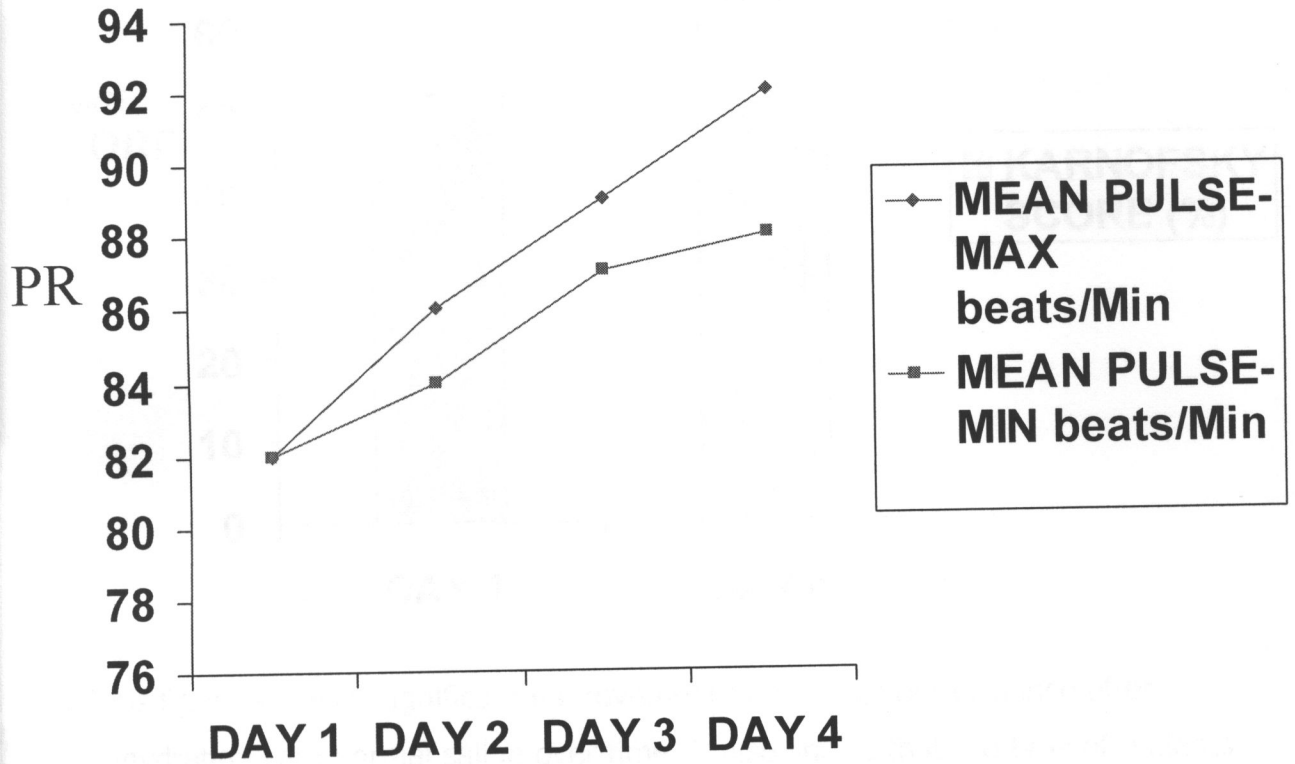
This figure shows a rise in blood pressure over time in standing position. There was no fall in blood pressure when immediately measured from the lying position. This indicates absence of postural hypotension in these patients, but sometimes fall in BP may be delayed.

FIGURE 6. COMPARISON OF MEANS OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURES FROM LYING TO STANDING POSITION.



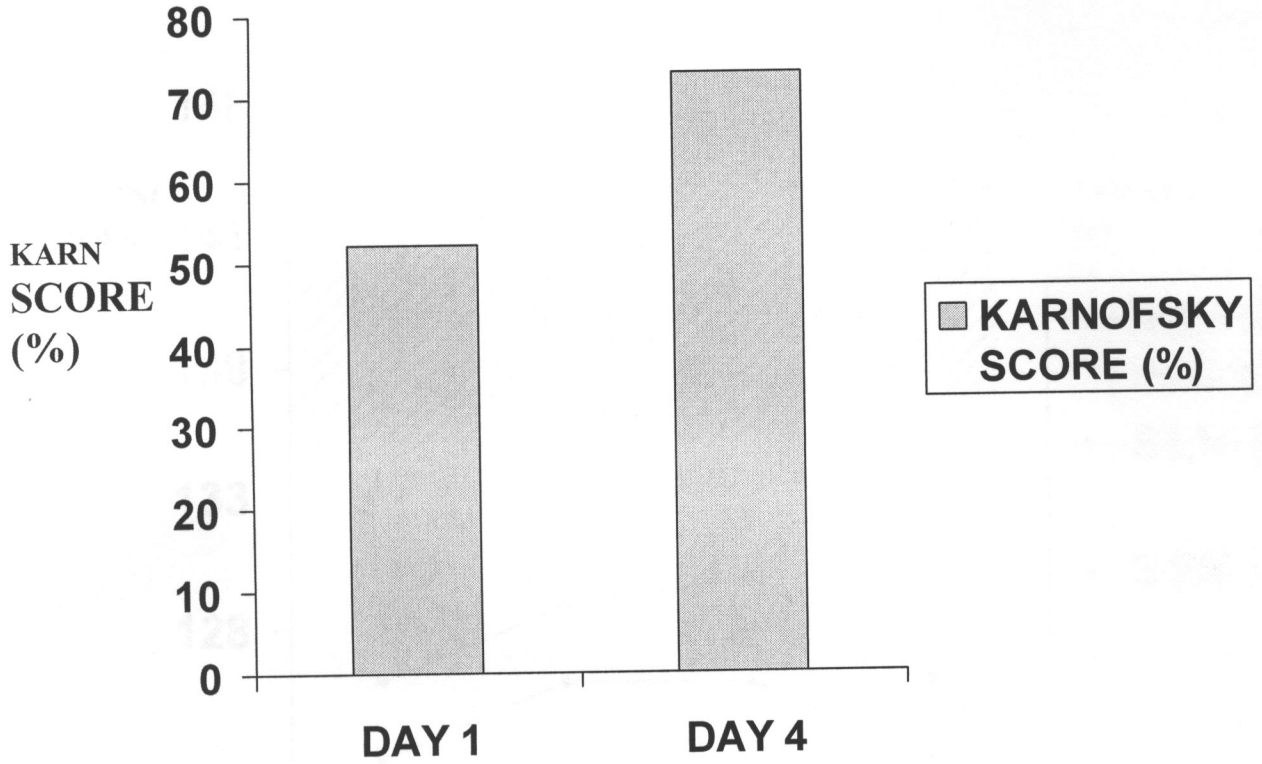
This figure shows a normal observed phenomenon, that blood pressure in standing position is higher than in lying position. Our patients showed a normal response signifying that volume depletion was either well compensated with time or the patients blood pressure regulatory mechanism was still functioning well.

FIGURE 7. MAXIMUM AND MINIMUM PULSE RATE IN DEEP INSPIRATION IN LYING POSITION.



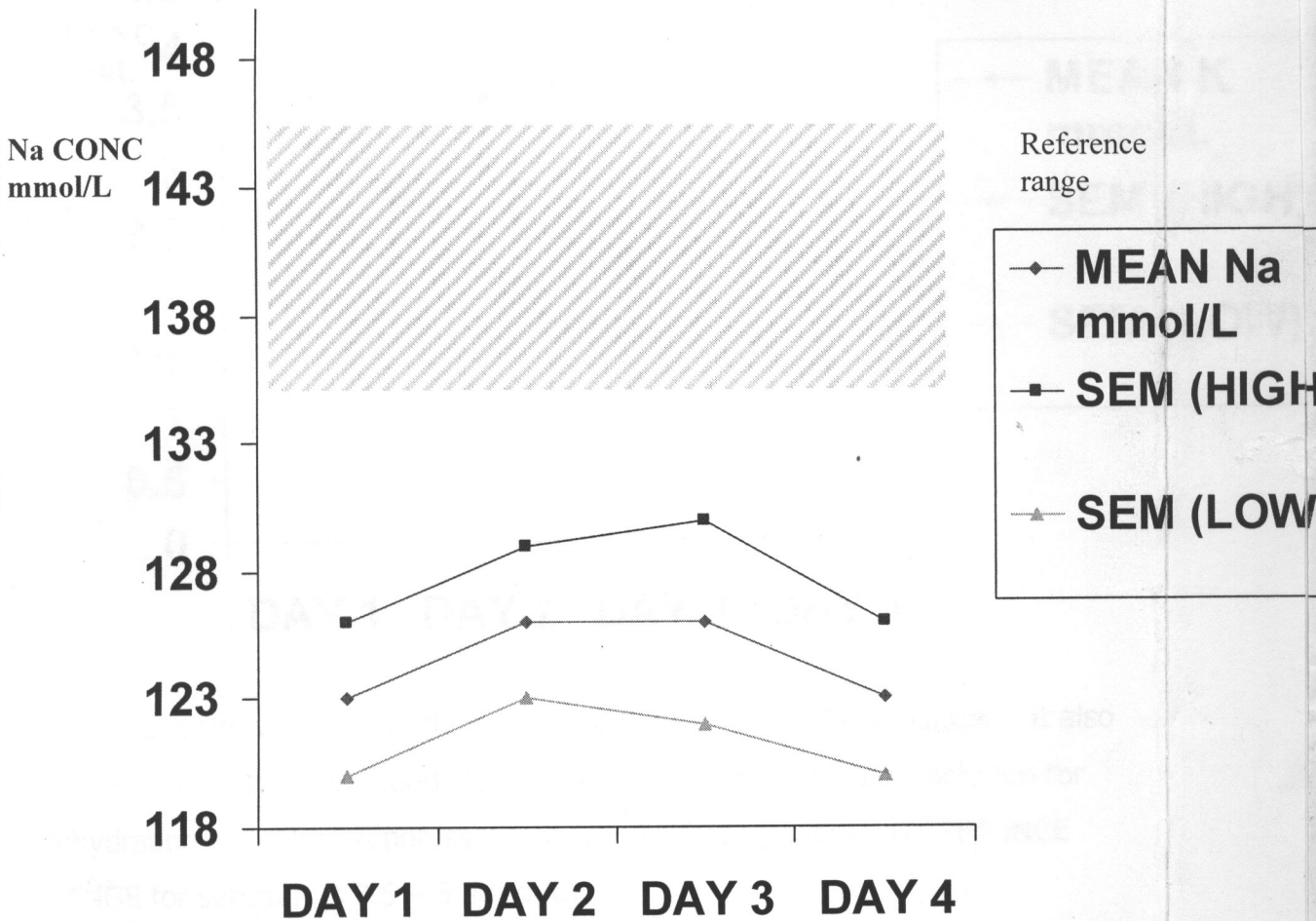
This figure shows an increase in pulse over time, but with no tachycardia.

FIGURE 8. PATIENTS RESPONSE AND PERFORMANCE BY KARNOFSKY SCORE.



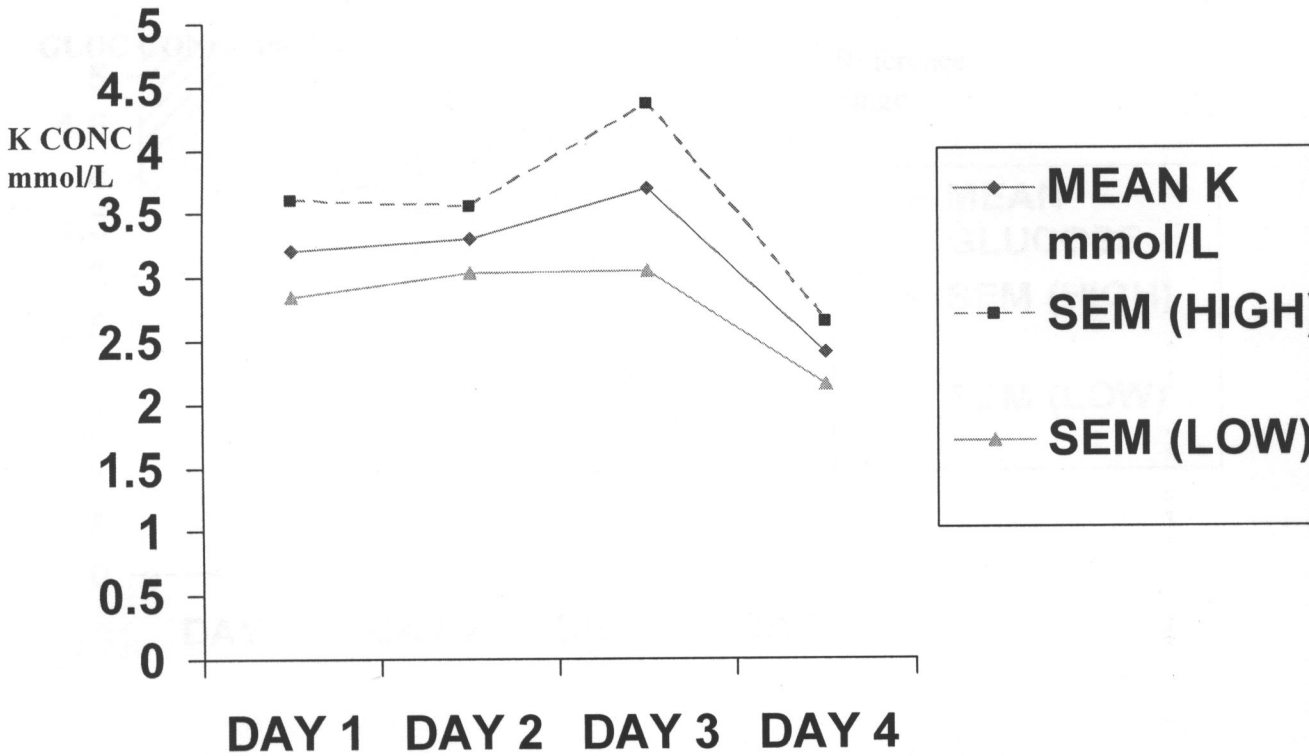
This figure shows a significant improvement in personal performance after rehydration with normal saline over time. It also shows that the type of patients chosen for the study over the three days of monitoring were not completely bed ridden.

FIGURE 9. SERUM SODIUM (Na) OVER PERIOD OF MONITORING.



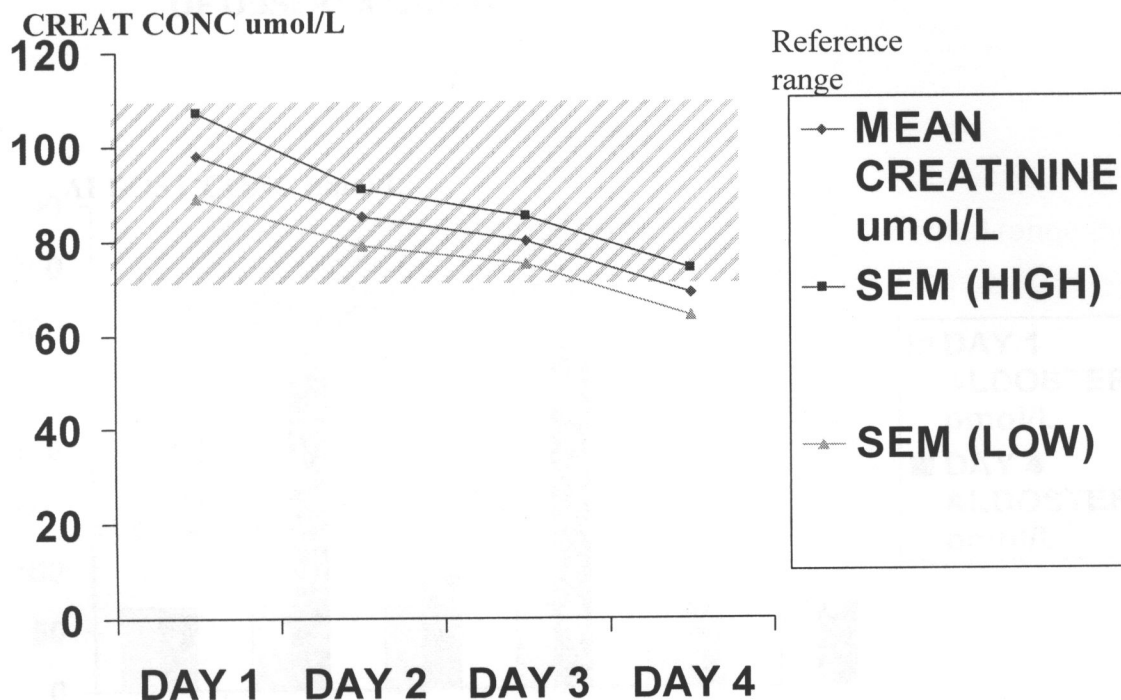
This figure shows significantly low serum sodium levels in our patients. The low sodium did not improve towards the reference range in spite of the replenishing with 3 litres of normal saline every day. (REFERENCE RANGE for serum Na is 135 – 145 mmol/L)

FIGURE 10. SERUM POTASSIUM OVER PERIOD OF MONITORING.



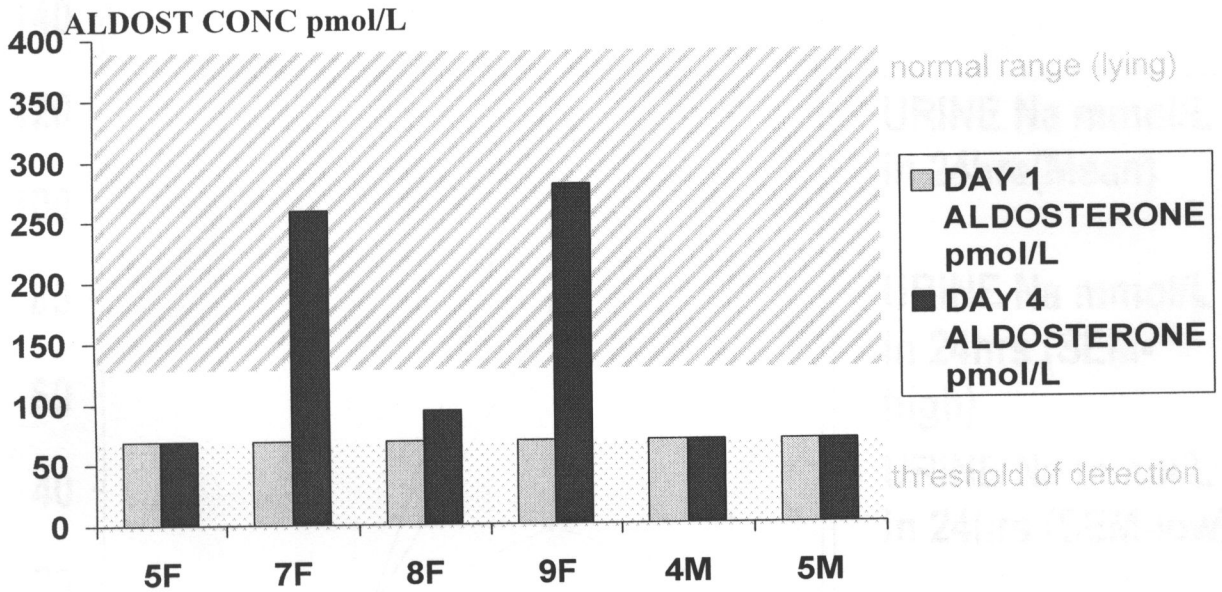
This figure shows significantly low potassium in serum of our patients. It also showed that potassium needs to be added to the normal saline solution for rehydration to replenish potassium deficits in these patients. (REFERENCE RANGE for serum K is 3.5 – 5 mmol/L)

FIGURE 12. SERUM CREATININE OVER PERIOD OF MONITORING



This figure shows a fall in serum creatinine over time. This could indicate increased renal excretion due to fluid load that improved the renal blood flow hence the glomerular filtration pressure and rate. It could also mean haemodilution effect as a result of rehydration with normal saline. Note that in the presence of malnutrition, the creatinine would be low due to reduced muscle mass. (REFERENCE RANGE OF CREATININE is 50 – 140 umol/L)

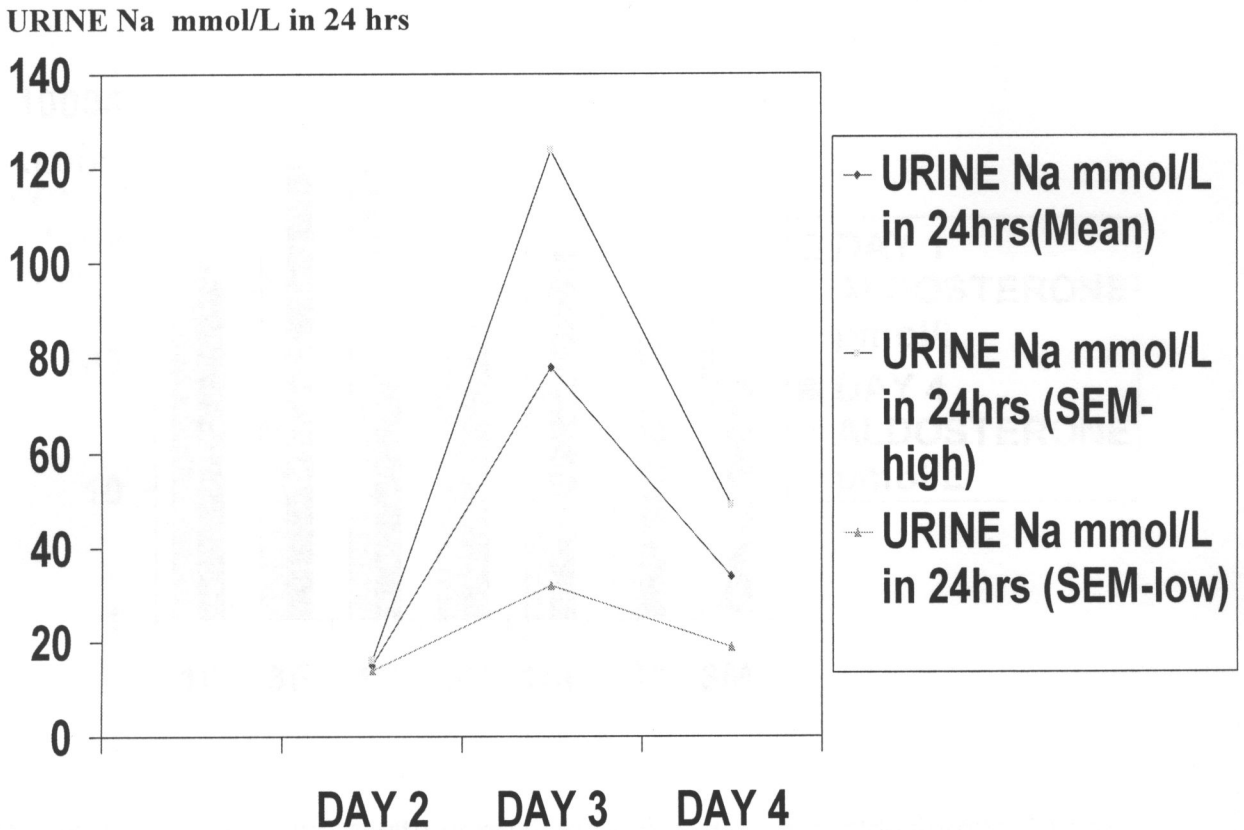
FIGURE 13. ALDOSTERONE SECRETION IN ADRENAL FAILURE PATIENTS. MONITORED FROM BASELINE (DAY 1) TO END OF OBSERVATION (DAY 4).



This figure shows patient undetectable aldosterone before the fluid load indicating adrenal insufficiency. Only two patients showed significant aldosterone secretion or concentration after fluid load of 3 litres normal saline over three days.

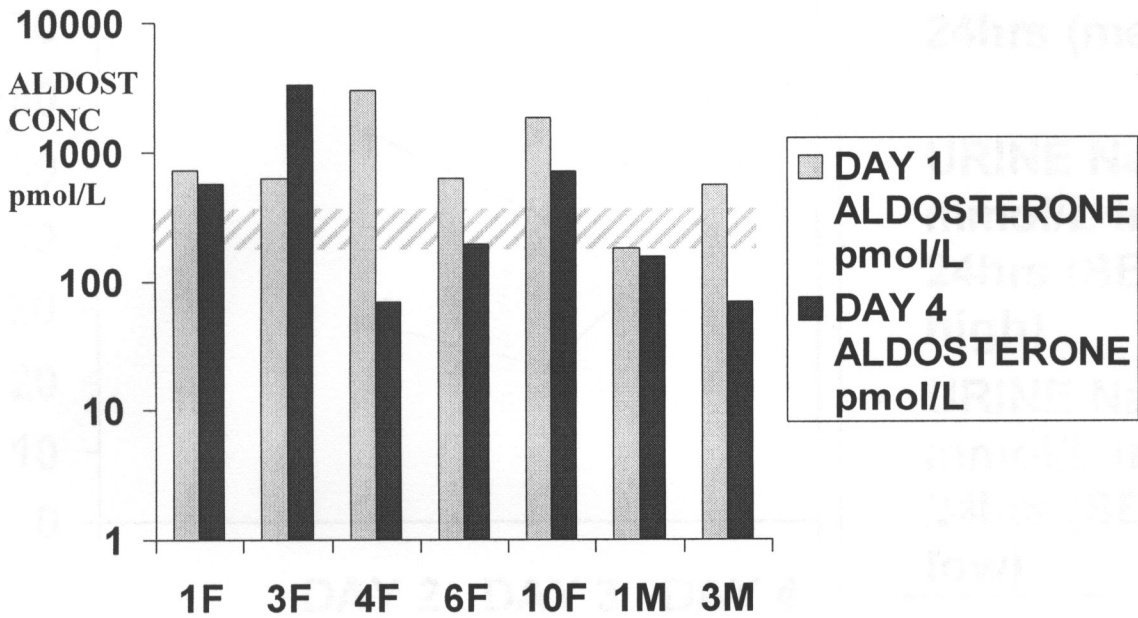
(REFERENCE RANGE FOR ALDOSTERONE IN LYING POSITION is 135 – 400 pmol/L)

FIGURE 14. SODIUM EXCRETION IN URINE IN ADRENAL CORTICAL FAILURE.



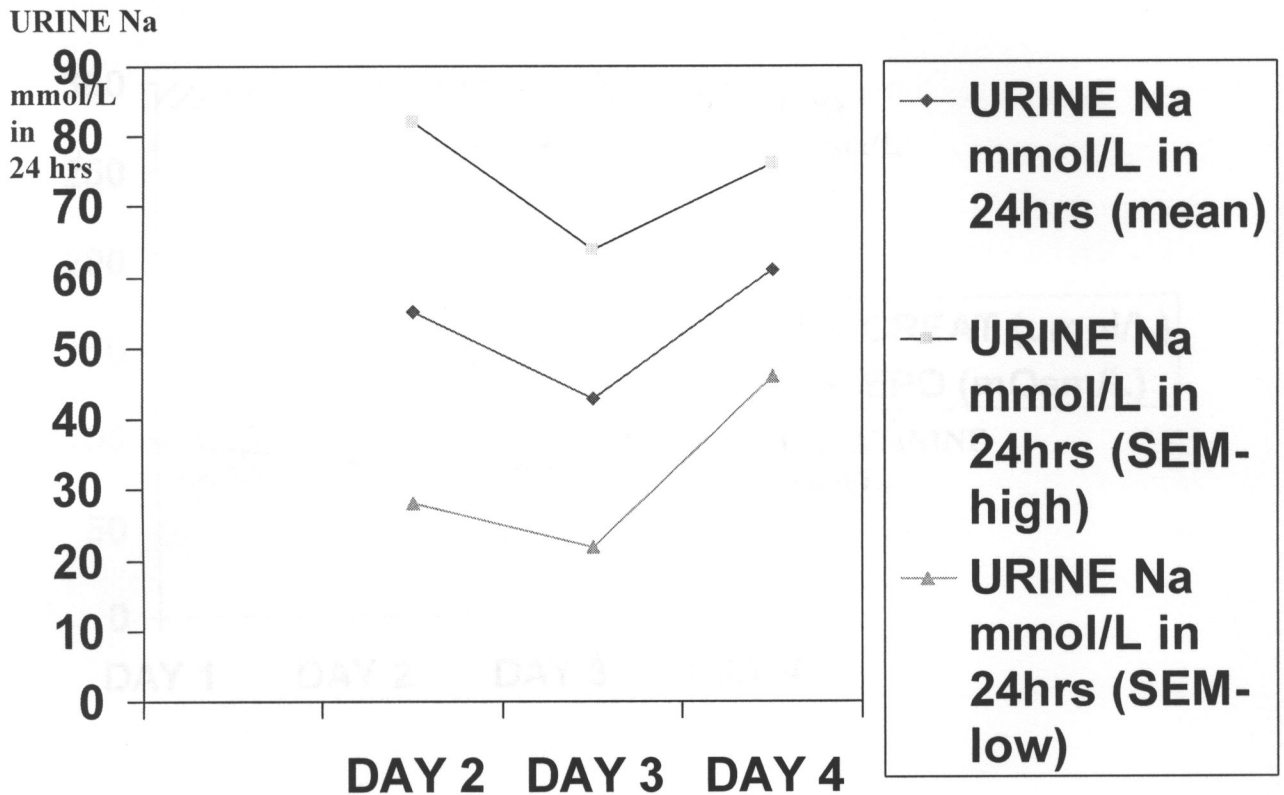
This figure shows uncontrolled sodium loss in urine in patients with adrenal insufficiency. In these patients, in face of low serum Na concentration, renal conservation of Na would be expected.

FIGURE 15. ALDOSTERONE SECRETION IN NORMAL ADRENAL CORTICAL FUNCTION (IN LOGARITHMIC SCALE) FROM BASELINE (DAY 1) TO END OF MONITORING (DAY 4).



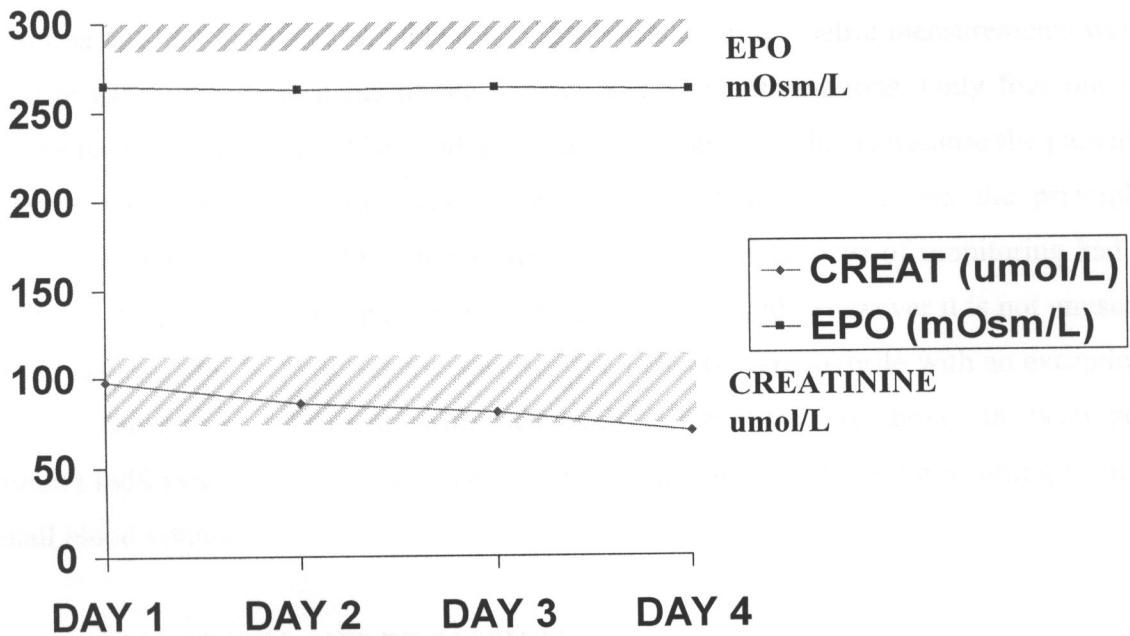
This figure shows patients with normal adrenal secretion of aldosterone. There was a reduction in aldosterone in all but two patient after blood volume replenishing with normal saline. This is expected in normal adrenal function in these patients although in 1F and 10F aldosterone still doesn't fall into normal range.

FIGURE 16. SODIUM EXCRETION IN URINE IN NORMAL ADRENAL CORTICAL FUNCTION.



This figure shows a controlled urine sodium excretion after fluid load over time. This indicated normal adrenal function.

FIGURE 17. EFFECTIVE PLASMA OSMOLARITY (EPO) AND CREATININE OVER PERIOD OF MONITORING.



This figure shows a fall in serum creatinine over time and a consistently low EPO. This indicated that the cause of low EPO was more likely due to sodium and water loss than due to water retention as a result of renal failure. The patients had hyponatraemic hypoosmolar type of dehydration.

CHAPTER 5

5.0 DISCUSSION OF FINDINGS

5.1 NUTRITION STATUS AND VITAL OBSERVATIONS

Baseline data are presented in table 1 and 2 to show anthropometric measurements were used to assess nutrition status of the patients and vital observations. Only four out of twelve patients had a Body Mass Index below 20 Kg per m². This is because the patients selected were not necessarily wasted but that persistent diarrhea was the principle selection criterion. One of the patients who survived the four days of monitoring had a BMI of 7.8 Kg per m². This patient was exceptionally wasted. However it is not unusual to see patients at UTH with severe wasting. The patients were afebrile with an exception of two. There were no patients with tachycardia (with pulse rate above 100 beats per minute) indicating that the patients had adapted to the hypotensive state resulting from a small blood volume.

5.2 SERUM SODIUM AND POTASSIUM

Table 3 shows some baseline concentrations for serum electrolytes. There were 9 out of 11 patients with low serum sodium, 9 out of 10 patients with low serum potassium. This is indicative of the chronic loss of the electrolytes from chronic diarrhea and vomiting, and perhaps reduced intake due to lack of appetite. AIDS patients often complain of dysphagia and nausea coupled with lack of appetite for food. These make replenishing of lost nutrients and salts difficult. In the short term salt and water depletion leads to postural hypotension and hypovolemic shock. In these patients, there was no evidence of postural hypotension as can be seen from figures 2 to 6, and their abnormality is probably best thought of as Na⁺ and K⁺ depletion. The low serum sodium and potassium probably resulted from intestinal losses in the presence of adrenal failure.

The serum electrolyte concentrations did not return to normal with a daily 3 litres of normal saline but they did improve. It is clear that fluids as normal saline with added

potassium would be necessary in fluids used for replacing salt loss. Addition of potassium without monitoring would have been dangerous in only one of our patients who had overt renal failure because of the danger of hyperkalaemia. A plasma potassium concentration of 3.0mmol/L generally implies a potassium deficit of about 300mmol. If potassium supplements are given intravenously, they should be thoroughly mixed with normal saline. The added potassium should not exceed 140 mmol/24hours.

It is important to note that even severe hypokalaemia may be asymptomatic. If symptoms are present, they are related to disturbances in neuromuscular function such as muscle weakness, constipation and paralytic ileus. Further more perhaps 4 to 6 litres of such fluids would be necessary on admission in order to replenish the depleted volume. This could be maintained at 3 liters as daily requirement. None of our patients showed any signs of fluid overload and even wasted patients tolerated high percentage of body weight infused as saline. Also these patients had diarrhea thus ongoing losses.

5.3 PRESENCE OF HYPOGLYCEMIA

All the patients with PDM presented with low levels of serum glucose on admission (figure3). The glucose levels increased slightly to lower levels of normal over the four days of monitoring. This could indicate an improvement in the patient's condition which made them tolerate some food intake. This finding supports the argument that PDM patients are at high risk of hypoglycemia due to both nutrient loss secondary to malabsorption or reduced food intake secondary to dysphagia, nausea and vomiting. The hypoglycemia could also be due to low glucocorticoids which are secondary to adrenal failure damaged by opportunistic infection (91). The PDM patients should therefore be given some glucose infusion as part of treatment on admission.

5.4 HYDRATION STATUS

Apart from the low sodium and potassium that these patients presented with, they had low effective plasma osmolarity (EPO). The serum creatinine was normal in most patients indicating that they had no acute or chronic renal failure, although it should be

recognized that in such patients with wasting, normal creatinine may not imply normal renal function because of reduced muscle mass. The low EPO was a direct result of hyponatremia secondary to water and electrolyte loss (81). The EPO did not improve to normal over the period of monitoring in spite of fluid replacement. This suggests that the sodium replenishment was not enough during the four days and that the patients were still deplete in water and sodium even after the 9 liters of normal saline. This could have been compounded by continued water and electrolyte loss due to the diarrhea. Ineffective control of EPO leads to continued water loss making rehydration difficult. Adrenal failure leads to inappropriately low glucocorticoid and mineralocorticoid secretion, and management of water and electrolytes in these patients becomes very difficult. It could therefore be important to add corticosteroids in these patients as part of treatment to restore homeostasis.

These patients have a hyponatraemic type of dehydration which could be corrected by a fluid high in sodium, such as 3% saline. The serum sodium defines the need for water (82,83) but it is not a guide to the prescription of saline (83). Hyponatraemia should be corrected by 8 mmol/L of sodium in saline per day or less (84). Faster rates of correction offer no benefit, and increase the risk of osmotic demyelination.(84,85,86). Before giving intravenous saline solutions, dietary sodium should be liberalized and oral salt encouraged. This could be encouraged especially with patients on home based care strategy. In patients with hyponatraemia caused by hypovolemia, such as ours in the study, isotonic saline is effective therapy. But too much saline may initiate a large water diuresis, causing the serum sodium concentration to increase by much more than intended (86). We observed no such increase, further suggesting that the amount of fluids given were inadequate.

It has been suggested that a small amount of hypertonic saline (3 % saline) is a better treatment for hyponatraemia than the indiscriminant infusion of large volumes of isotonic saline. Hypertonic saline infusion of 1 ml of 3 % per Kg body weight per hour can be expected to increase the serum sodium by 1 mmol/hour initially. In less urgent cases a carefully monitored infusion of 3% saline at approximately 0.2 mL per Kg body weight per hour could be used to carefully increase the serum sodium concentration by no more than 8 mmol/L per day (87). Most of our (PDM) patients at UTH weigh an average of 40-

50Kg, it would therefore mean that the majority of our patients would benefit from 8 to 10 mL of 3% saline infusion administered within the first hour to replenish serum sodium. However the practicability of this infusion at UTH given the nursing manpower shortage is doubtful and could be dangerous. It is important to note that patients who are ill often have non-osmotic stimuli for the release of vasopressin, which causes water retention and hyponatraemia as the commonest electrolyte disorder in chronically ill and hospitalized patients (88).

5.5 EVIDENCE OF ADRENAL CORTICAL FAILURE

In the presence of hyponatremia or salt depletion or volume depletion, the normal physiological response is activation of the rennin-angiotensin-aldosterone cascade. However, in our patients, aldosterone levels were not elevated and indeed in six of our patients it was undetectable (figure 13) in the presence of hyponatremia and volume depletion (table 3). Serum aldosterone activity was much lower than normal. And only two of these patients had an increased aldosterone activity above normal after daily 3 litres fluid challenge. Furthermore, average sodium excretion in urine was irregular and high, above 20 mmol/day, and in some instances above 60mmol/day (figure 6). This inability to control sodium excretion in urine is another factor to support the possibility of existence of adrenal insufficiency.

Adrenal cortical failure has been a well known complication of AIDS since the onset of the epidemic (90,91), but adrenal insufficiency is usually asymptomatic (89). It is known that the Human Immunodeficiency Virus affect adrenal secretion as a result of polyclonal B-cell activation and the production of anti-adrenal cell antibodies (92). Opportunistic infections which are common in AIDS patients also affect adrenal glands. Such infections include Cytomegalovirus (40-80%) (93), Mycobacterium avium and tuberculosis, Kaposi's sarcoma, and Toxoplasmosis gondii (4-12%) (94,95). Further research based on histological findings of adrenal glands at autopsy could be carried out to determine the spectrum of adrenal infections at UTH, Zambia.

The other six patients showed normal adrenal function. There was a slight reduction in aldosterone activity consistent with the daily fluid challenge over the four days of

monitoring (figure 7). These patients also showed a good control of sodium excretion in urine over the four days of monitoring (figure 8). Urine sodium excretion was just about 50 mmol/day from day 2.

5.6 RELATIVE HYPOTENSION BUT NO EVIDENCE OF POSTURAL HYPOTENSION.

The patients exhibited relative hypotension in both lying and standing positions in their diastolic and systolic blood pressures (figures 2 to 6). This is consistent with their chronic fluid loss which makes them have a relative shrunken blood volume. The patients also showed an increase in both systolic and diastolic blood pressures over the period of monitoring. This showed that daily appropriate fluid replacement is essential for maintenance of adequate blood pressure (figures 2 to 6).

However, the patients did not show any evidence of postural hypotension from the lying to the standing position (figure 6). The systolic and the diastolic blood pressures did not fall with upright state. Blood pressure was measured immediately so late falls in blood pressure may have been missed. This may indicate a degree of adaptation to the adrenal insufficiency in these patients. This is consistent with a study which showed that AIDS patients with adrenal insufficiency lacked specific clinical features, such as postural hypotension, for the adrenal failure, other than an inadequate synacthen stimulatory test (89).

The patients exhibited an increase in the pulse rate following hold of their deep inspiration. This shows that the cardiovascular system mechanism for regulation of blood pressure were still functioning and there was no evidence of loss of autonomic control of BP (figure 7). An additional factor is that these patients had already received some treatment in UTH.

5.7 PATIENTS PERFORMANCE AND RESPONSE FOLLOWING FLUID CHALLENGE.

The patient's performance and response following fluid challenge was good. They improved in their clinical status by an average of 30 points on the Karnofsky score (figure 15) within three days. This showed that daily fluid challenge was important in improving the quality of life of patients with PDM. It is therefore important to vigorously replace appropriate fluids in patients with PDM so as to maintain a quality life and improved blood pressure (figures 11, 12, and 13).

The fact that these patients were able to improve clinically within three days means that adequate appropriate fluid replacement in PDM would drastically reduce hospital stay and reduce hospital budget. It would also mean that the PDM patients would be able to be sent home early, within three days, with less risk of readmission. However, selection of intravenous fluid therapy is imperative to prevent brain cell oedema due to worsening hyponatraemia. Cerebral oedema is especially likely to develop in children, in the malnourished individuals and in old age. Wasted individuals (PDM) have reduced skeletal mass which means also a direct proportion of reduced body water content. This means that excess water collects in the extravascular fluid compartment predisposing these patients to cerebral oedema with acute occurrence of hyponatraemia(82-86).

CHAPTER 6

6.0 CONCLUSIONS

This pilot study has demonstrated that AIDS-related persistent diarrhea causes water and electrolyte losses which are not being adequately replaced at UTH medical admission wards. It has also shown that, about half of the PDM patients present with adrenal insufficiency. Adequate rehydration with appropriate fluids can improve the quality of life and blood pressure of these PDM patients.

6.1 RECOMMENDATIONS

This pilot study has been able to highlight some basic flaws in our management of PDM patients. Although its discussion is based on 12 patients, certain inferences can be drawn and in some instances further studies done to justify certain practices hereby recommended. The following recommendations are therefore made in the approach to the clinical management of PDM patients at UTH:

1. Given that the PDM patients have a serious deficit in sodium and potassium blood levels, it is recommended that the amount of fluid to be given to PDM patients should be high in potassium, and that 3 litres of Normal saline given especially on admission is inadequate to maintain blood effective plasma osmolarity which is important for maintaining adequate hydration. It is hereby recommended that 4 to 6 liters of normal saline thoroughly mixed with at least 140mmol/24hours of potassium be initiated on admission.
2. PDM patients present with hypoglycaemia on admission. I hereby recommend that the initial treatment should include an infusion of glucose solution given as a bolus dose on admission of PDM patients to contain their hypoglycemic status.
3. Half of our patients presented with adrenal insufficiency. I recommend that a formal clinical trial be carried out on the role of steroids for PDM patients. I am of the view that all PDM patients should benefit from an initial bolus dose of steroids (mineralocorticoid

or corticosteroid) on admission. This would help in maintaining normal sodium and potassium blood levels and reduce sodium loss in urine. The steroids would also help maintain blood pressure augmenting catecholamine effects observed in hypovolaemia. This would help all of PDM patients with adrenal insufficiency and those in hypovolaemic shock. Further research needs to be carried out by autopsy of wasted patients to determine the histological aetiology of adrenal failure.

4. This study has highlighted that fluid replacement alone can improve PDM patient's quality of life and blood pressure. We hereby recommend that an aggressive appropriate fluid regime should be initiated on admission to attain to adequate hydration. This would significantly help in reducing hospital stay, cost per bed space and it would also create the needed hospital space for other conditions.

APPENDICES

APPENDIX 1

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APPENDIX 2

WORK-PLAN

MONTHS	N	D	J	F	M	A	M	J	J
ACTIVITY									
Proposal write up	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
Approval									
Patient recruitment									
Data collection, sample analysis	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
Data analysis		xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
Report write up					xxxx	xxxx	xxxx	xxxx	xxxx
Dissemination of results								xxxx	xxxx

APPENDIX 3

BUDGET (IN KWACHA)

ITEM	UNIT COST	TOTAL
ECG	10,000	200,000
Na/K assays	free use of flame photometer	
Urea	20,000	400,000
Creatinine	20,000	400,000
Glucose	20,000	400,000
Blood sampling equipment	20,000	400,000
Antibiotics for patient care	20,000	400,000
Intravenous fluids (3 L each)	18,000	360,000
Cannulas	6,000	120,000
Nursing time (5 months)	600,000	3,000,000
Aldosterone	90,000	2,160,000
Stationery	400,000	400,000
Data analysis	00,000	500,000
<u>Total</u>		<u>7,940,000</u>

APPENDIX 4

QUESTIONNAIRE

A PILOT STUDY ON ELECTROLYTE AND WATER LOSSES IN PATIENTS WITH AIDS-RELATED PERSISTENT DIARRHOEA AND MALNUTRITION AT UTH

SERIAL NO. DATE:...../...../.....

STUDY NO. SERO STATUS

DAY 1. ON ADMISSION (BASELINE DATA)

AGE..... YRS SEX: M / F WEIGHTKG HEIGHTCM

TEMP..... °C RESPIRATORY RATE...../ MINUTE

PULSE IN DEEP INSPIRATION a) / MINUTE

PULSE IN DEEP EXPIRATION b) / MINUTE

0800HRS

BP a).....mmHg (LYING)
 b)mmHg (STANDING)

1600HRS

BP a).....mmHg (LYING)
 b)mmHg (STANDING)

ECG
.....

INTRAVENOUS LINE SECURED AND FLUSHED WITH 10mL/Saline: YES / NO

KARNOFSKY SCORE:

0900HRS: BLOOD FOR BLOOD TESTS: YES / NO

Na, K, UREA, CREATININE, ALBUMIN, RENIN, ALDOSTERONE, CORTISOL

URINE COLLECTION STARTED AT TIME

DAY 2 :

OVER LAST 24 HOURS

FLUID	INPUT (ml)	OUTPUT(ml)

FULL PHYSICAL EXAMINATION AT 08:00 AND 16:00H

ANY ABNORMALITIES DETECTED?

.....
.....

i) BLOOD PRESSURE

08:00 HmmHg LYING,mmHg STANDING

12:00 H.....mmHg LYING,mmHg STANDING

16:00 H.....mmHg LYING,mmHg STANDING

ii) PULSE RATE ON DEEP RESP: MAXIMUM(MAX), MINIMUM (MIN)

08:00H/ MINUTE , MAX/ MINUTE , MIN

12:00H/ MINUTE, MAX./ MINUTE, MIN

16:00h/ MINUTE, MAX/ MINUTE, MIN

09:00H : BLOOD FOR TESTS:

Na, K, UREA, CREATININE, ALBUMIN, GLUCOSE, RENIN,
ALDOSTERONE, CORTISOL

0700HRS: URINE [Na]

DAY 3 :

IVF	INPUT	OUTPUT :	YES/NO
	
	
	

FULL PHYSICAL EXAMINATION AT 08:00 AND 16:00H

ANY ABNORMALITIES DETECTED?

.....

.....

ANY FURTHER REHYDRATION REQUIRED? YES/NO

.....

iii) BLOOD PRESSURE

08:00 HmmHg LYING,mmHg STANDING

12:00 H.....mmHg LYING,mmHg STANDING

16:00 H.....mmHg LYING,mmHg STANDING

iv) PULSE RATE ON DEEP RESP: MAXIMUM(MAX), MINIMUM (MIN)

08:00H/ MINUTE , MAX / MINUTE , MIN

12:00H/ MINUTE, MAX. / MINUTE, MIN

16:00h/ MINUTE, MAX / MINUTE, MIN

09:00H: BLOOD FOR TESTS:

Na, K, UREA, CREATININE, ALBUMIN, GLUCOSE, RENIN,
ALDOSTERONE, CORTISOL

0700HRS: URINE [Na]

DAY4 :

IVF	INPUT	OUTPUT :	YES/NO
	
	
	

FULL PHYSICAL EXAMINATION AT 08:00 AND 16:00H

ANY ABNORMALITIES DETECTED? YES/NO

v) BLOOD PRESSURE

08:00 HmmHg LYING,mmHg STANDING

12:00 H.....mmHg LYING,mmHg STANDING

16:00 H.....mmHg LYING,mmHg STANDING

vi) PULSE RATE ON DEEP RESP: MAXIMUM(MAX), MINIMUM (MIN)

08:00H/ MINUTE , MAX/ MINUTE , MIN

12:00H/ MINUTE, MAX./ MINUTE, MIN

16:00h/ MINUTE, MAX/ MINUTE, MIN

09:00H: BLOOD FOR TESTS:

Na, K, UREA, CREATININE, ALBUMIN, GLUCOSE, RENIN,
ALDOSTERONE, CORTISOL

KARNOFSKY SCORE

RSEARCH ASSISTANT NAME.....

SIGN:

DATE://

APPENDIX 5

A PILOT STUDY ON ELECTROLYTE AND WATER LOSSES IN PATIENTS WITH AIDS-RELATED PERSISTENT DIARRHOEA AND MALNUTRITION AT UTH

INFORMED CONSENT FORM

INTRODUCTION

You are being asked to take part in the research study named above because you have persistent diarrhoea, which causes you to lose a lot of water and salt. This study will give you a minimum of 3 litres of water mixed with salt over 24 hours as we think this will lead to more rapid recovery in your well being. Before you decide whether or not to take part in this study, we would like to explain to you the purpose of this study, any risks to you and what is expected of you. If you agree to take part you will be asked to sign this consent or make your mark in front of someone. You will then be given a copy to keep. You should be aware that this study has been approved by the Research Ethics Committee of the University of Zambia, which is there to protect you.

PURPOSE OF THE STUDY

The purpose of this study is to see if additional water and salts, given into your veins, will make you feel better and stronger, and improve the blood test measurements which indicate that someone is very depleted in these essential substances.

PROCEDURES

After you sign the consent form and have had a chance to ask questions, you will undergo a full physical examination. We will then need to carry out an HIV test after you have had the opportunity to see a trained counsellor. Two table spoons of blood will be drawn from you for testing every morning for 4 days to measure these substances in the blood. This will tell us if the treatment has been adequate. We will also collect all of your urine every day for these 4 days to see whether your kidneys are working properly in response to the water and salts you are being given as treatment. On the second day, you will be given 3 litres of water and salts by a drip into a vein. This will be repeated on the third day if the response has been inadequate. We will monitor you carefully with blood pressure and pulse measurements every few hours throughout.

RISKS AND DISCOMFORTS

There will be few discomforts for you in this study. Pain may be experienced as we insert a needle in your veins for the purpose of giving fluids. The only significant, though very unlikely, risk is that 3 litres may be too much for your body and could lead to complications. This is why we monitor you carefully as is good practice when anyone receives such drip fluids. If this happens, the drip will be discontinued and then all known

interventions will be done to reverse the effects.

BENEFITS

By taking part in the study, related laboratory tests and other tests, or requirements that may be needed for your treatment will be met by the study fund. If we are right in what we think, you will recover much quicker than is usual, but it is also possible that the additional fluid may not help you. You will receive care in terms of treatment for your diarrhoea even, in the event of your withdrawal from participation in the study.

CONFIDENTIALITY

Your research records will be confidential to the extent permitted by law. You will be identified by code and personal information will not be released without your written permission, except when required by law. The Ministry of Health, Central Board of Health, the University of Zambia Research Ethics Committee or School of Medicine may review your records, but again this will be done confidentially.

PLEASE NOTE

1. your participation in this research is entirely voluntary
2. you may decide not to take part or to withdraw from the study any time without losing the benefits of medical care at the hospital.

PERSON TO CONTACT FOR PROBLEMS OR QUESTIONS

Dr. T. Kaile, UTH/UNZA, Dept. of Internal Medicine, Lusaka.
P.O. Box 50110, Lusaka. Tel: 095 752291

.....

CONSENT TO JOIN THE STUDY

NAME

HAVING BEEN FULLY INFORMED ABOUT THIS STUDY AND ABOUT THE BENEFITS AND RISKS, I AGREE TO PARTICIPATE WILLINGLY.

SIGN DATE/...../.....

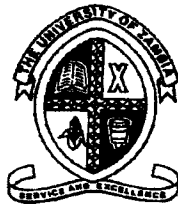
THUMBPRINT.....

WITNESS NAME..... SIGN.....

APPENDIX 6

KARNOFSKY SCORE : PERFORMACE STATUS

DEFINITION	%	CRITERIA
Able to carry on normal activity And work, No special care is Needed.	100	Normal, no complaints; no evidence of disease
	90	Able to carry on normal activity; Minor signs or symptoms of Disease
	80	Normal activity with effort; some signs and symptoms of disease
Unable to work, able to live at Home, care for most personal Needs, a varying amount of assistance is needed.	70	Cares for self, unable to carry on normal activity or to active work
	60	Requires occassional assistance, but is able to care for most of his needs.
	50	requires considerable assistance and frequent medical care
Unable to care for self. Requires Equivalent of institutional or Hospital care. Disease may be Progressing rapidly.	40	Disabled, requires special care assistance.
	30	Severely disabled; hospitazation is indicated although death not imminent.
	20	Very sick, hospitalization necessary; active supportive treatment necessary.
	10	Moribund; fatal process progressing rapidly.
	0	Dead



THE UNIVERSITY OF ZAMBIA

RESEARCH ETHICS COMMITTEE

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Ref: 003-07-03
24 December, 2003

Dr T. Kaile, BSc (HB), MBChB, MSc, PG Dip
School of Medicine
University of Zambia
P.O. Box 50110
LUSAKA

Dear Dr Kaile,

RE: SUBMITTED RESEARCH PROPOSAL

The following research proposal was presented to the Research Ethics Committee meeting on 30 July, 2003 where changes were recommended. We would like to acknowledge receipt of the corrected version. The proposal has now been approved. Congratulations!

Title of proposal: 'A pilot study on electrolyte and water losses in patients with AIDS-related persistent diarrhoea and malnutrition at UTH'

Conditions:

- This approval is based strictly on your submitted proposal. Should there be need for you to modify or change the study design or methodology, you will need to seek clearance from the Research Ethics Committee.
- If you have need for further clarification please consult this office. Please note that it is mandatory that you submit a detailed progress report of your study to this committee every six months and a final copy of your report at the end of the study.

Yours sincerely

Prof. J. T. Karashani, MB, ChB, PhD

CHAIRMAN

RESEARCH ETHICS COMMITTEE

Date of approval: 24 December, 2003

Date of Expiry: 23 December, 2004

Please note that when your approval expires you may need to request for renewal. The request should be accompanied by a progress report (Progress Report Forms can be obtained from the Secretariat).