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# Assessment of Intracellular and Extracellular Fluids (ICG, ECf) Compartments with Antimal, Chloroquine, Coartem, Fansidar and Malareich

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**ABSTRACT**
Quantitative assay with spectrophotometer was used in the determination of plasma sodium, potassium and chloride concentration in the administration of antimal, chloroquine, coartem, fansidar and malareich antimalaria drugs. In the antimal group there was no significant difference in the sodium, potassium and chloride concentration in the plasma when compared with control ($P>0.05$). Also in the chloroquine group, the sodium and chloride concentrations were not significantly different from the control ($P>0.05$). However, there was low concentration of potassium which was significant when compared with control ($P<0.05$). In the Fansidar administration there was no significant difference in sodium, potassium and chloride concentration when compared with control, ($P>0.05$). Also in the malareich group, the sodium and chloride concentrations showed no significant difference with the control ($P>0.05$). But there was significant difference in potassium concentration when compared with control ($P<0.05$). The study observed that chloroquine and malareich therapy affect extracellular fluid compartment of the body and induced hypokalaemia which may result in deficit cell membrane potential and the related general body muscle weakness.
**Keyword:** Hypokalaemia, antimalarials, ICF, ECF.

## INTRODUCTION

The maintenance of constancy of body fluids is very necessary for normal body functioning and such stable constancy is also very essential for homeostasis. The body fluids composed mainly of water and electrolytes as solutes distributed in the intracellular and extracellular (ICF & ECF) compartments. The ICF are fluids found within the cells while the ECF are those outside the cells. The extracellular fluid compartment is further split into interstitial fluid and the blood plasma. However, there are the specialized type of extracellular fluids such as synovial, peritoneal, pericardial, cerebrospinal and the intraocular (Guyton & Hall 2006), Bell, Smith & Paterson, 1980). The constancy of the body fluids is achieved through exchange of fluids and electrolytes between the ICF and ECF.

The electrolytes in the fluid are differently distributed in the intracellular and extracellular fluids due to Donnan and plasma proteins effects, (Guyton & Hall, 2006). For instance, the concentration of positively charged ions (cations) is slightly higher in the plasma than in the interstitial fluid of the same extracellular fluid. This is explained based on the negative net charge on the plasma proteins which attract positively charged cations e.g sodium, potassium into the plasma. On the other hand, the anions with negative net charges are repelled by the negatively charged plasma proteins and so are more in the interstitial fluid. But in practice such concentrations are same between the two compartments through regulating mechanism e.g. the kidneys. But the basic regulatory system is by the cell membranes which are highly permeable to water but less to electrolytes. For instance potassium, phosphates are in large quantities in the ICF while moderate quantities of magnesium, sulphate are also found. But in the ECF are found mainly sodium, chloride, however, trace amounts of these are found in the ICF. Thus, the differences in the ionic composition of the ICF and ECF is first the cell membrane selectivity, cum integrity, the pump system, the active transport and energy requisition. The disbalanced of these factors derail the fluid components and the resultant negative physiology (Oyebola, 2002). Sodium ions form about 90% of 154 mmol/L of inorganic cation in the ECF. It is responsible for maintaining normal distribution of water and osmotic pressure in the ECF. Its normal concentration in the body is 136-145mmol/L, (Baron, 1998). It is present in the diet at 130-360mmol i.e. (815g) of sodium as sodium chloride is absorbed daily in the gastrointestinal system. But the body requires only 1-2mmol/day. The excess is excreted by the kidney. Low level of sodium is expressed clinically as hyponatremia

 

which may be associated with envolemia which is low sodium at normal ECF or decrease sodium (hypovolemia) or increase sodium (hypervolemia) or increase cellular fluid. But hyponatremia is often due to dilution independent of the body water and ECF, (Andy, 1999). Sodium loss may result from exudation through skin in burns situation or through sweat e.g. heat. It could be lost through gastrointestinal tract secretion, fistulae, vomiting, diarrhea, (Hihnala, 2006), chlorea and intestinal aspiration, (Canani, 2004).

Increase in sodium can also occur as hyponatremia which occurs when water intake is less than the sum of renal and extra-renal water loss. Its also occur in situation which increase in the concentration of non solute in the ECF raised the serum osmolality and also promote renal water loss and osmotic diuresis (Anderoli 1982). Hypernatraemia is also associated with high sodium chloride intake and low excretion which may complicate hypertension. There is also genetic transport disorders with chloride, (Kere, 1999).

Potassium is mainly present in the ICF and very low in the ECF but can be determined in the ECF. The normal concentration is 3.5-5.2mmol/L. The body contain about 35000 meq/Lg which 85 meq/L is extracellular in context. The high concentration in ICF is due to the fact that potassium diffuse slowly outward through the cell membrane as $Na^+$ - $K^+$ ATpase pump continue to transport potassium into the cell. (Giebisch, 1996).

The physiologic roles of potassium is in the regulation of muscular activities through generation of action potentials and nerve impulse transmission, (Burton, 2000). Plasma potassium is regulated by $Na^+$ - $K^+$ ATpase which affects membrane transpiration and leakages. But the pH of the ICF and ECF of the potassium favours either alkalosis or acidosis, for instance renal potassium wasting in alkalosis and retention in acidosis (Nuhamchan, 1996). However, hypokalaemia which is total reduction in potassium concentration occurs when renal and extra potassium losses exceed potassium intake. But hyperkalaemia which is increase in plasma concentration may be caused by multiple factors (Walmsey, 1984). It is mainly developed when potassium intake exceeds the sum of renal extra potassium losses, (Riemanschneider, 1983).

Chloride is found mainly in the ECF often associated with potassium and sodium. The normal body concentration 96-108mmol/L and 130-199meq/L in the spinal fluid (White, 1976) in the intracellular erythrocyte it is 44-54mmol/L. Chloride ions are found in food and absorbed in gastrointestinal tract. But its excretion is higher than sodium indicating the higher dissociation property of this action. The Daily intake is 200mmol/L (7g) excess is excreted in urine and in sweat. There is association of hyper and hypo chloremia with renal tubular acidosis, decreased $CO_2$ content and hypokalaemia, (Ethier, 1990, Tolins, 1982). The hyperchlorema may also be associated with high salt intake and saline infusions as in intravenous drips. Antimal and malareich are preventive antimalarials of same constituents as fansidar. Coartem is curative with artemeter and lufantrine combination. The drugs are alternative for chlorquine and fansidar resistant malaria.

The interactions between the intracellular and extracellular compartment and the antimalarial drugs are imperative areas of physiologic concern. This is because the antimalaria as drugs often bind with the plasma proteins so as the electrolytes. These competitive interactions may result in an inhibitory system which may develop to favour the binding of some substances of physiologic need than the other. This is why the study was initiated particularly to compare such competitiveness with respect to the old and the new antimalarials. A physiologic model of this type will go along way to sieve the active, cell and organ friendly antimalarials from the substandard ones without actually analyzing the active ingredients. This is necessary in the face of old drugs with new names. Physiologic validation of antimalarials would enhance the pathophysiology of malaria and pathologic effects of drugs to be on course in forming good logistic approach in malaria disease management.

## MATERIALS AND METHODS

**Animals:** A total of thirty (30) albino rats obtained from stock in the University of Uyo, Faculty of Pharmacy animal house were used for the study. Right for the use of the animals was not obtained as there is no animal right organization where the study was done, however, the animals were not tortured during the study. The animals were divided into five drugs groups with six (6) animals in each drug group including control.

**Drugs Administration:** Five antimalaria drugs, antimal®, chloroquine® coartem®, fansidar® and malareich® were used. The drugs were purchased in a registered pharmacy shop where the study was done. The drugs were administered according to the methods of (Bertram, 2004, Robert, et al. 1979). But briefly the drugs were given per weight of each animal orally using canula by-passing the esophagus and delivered into the stomach. But it was derived from the average weight of man, (70kg) and given also based on the preventive and curative dosages. The

electrolytes concentration, sodium, potassium and chloride in the plasma were monitored for 28 days adopting the WHO, 1982 model for monitoring antimalaria drugs efficacy and parasite clearance. But in our study malaria parasites were not given to the animals.

**BLOOD AND PLASMA COLLECTION**

Blood samples were collected from the animals by cardiac puncture through anesthesia with chloroform (Dacie & Lewis 2007). The blood samples were spun immediately after collection at 1200rpm for 10mins and analyzed for the electrolytes using spectrophotmetry and electrometric methods.

**SPECTROPHOTOMETRY AND ELECTROMETRIC TITRATION**

For sodium and potassium, spectrophotometery methods was used to determine the concentrations in the plasma but for the chloride, electrometric titration method was used (Reitman, Frankel, 1975).

**Sodium:** (Principle) sodium in the supernatant precipitated in magnesium and Uranyl acetate respectively and ammonia thiolycolate in sodium leading to the formation of yellowish, brown coloration. The absorbance difference between the reagent blank (without the sodium precipitation) and the result of the analysis would be proportional to the concentration of the sodium at 550nm Wavelength. The indepth working methods was based on the author's and manufacturers instructions, here refers.

**Potassium:** (Principle) A colloidal suspension formed in the mixture of potassium in the test sample with sodium tetraphenyl boron form turbidity such which is proportional to the concentration of the potassium as the absorbance increase or decreases at 500nm wavelength. The assay was done according to manufacturers instructions.

**Chloride:** (Electrometric method). The test samples placed in electrochemical cell system receive silver ions through electrolysis to form silver chloride which precipitated until all the chloride ions are removed from the solution through this process, the increase in potential with salts ions will shut off the instrument and the time taken for such potential to act on the instrument measures the concentration of chloride in the plasma. The general application of the method was according to the author's and manufacturers instructions here refers.

**RESULTS**

**Table 1: Effect of antimal, chloroquine, coartem, fansidar and malareich on plasma sodium, potassium and chloride.**

| Control & Drugs | $Na^+$ | $K^+$ | $Cl^-$ |
|---|---|---|---|
| Control | 139.4±0.06 | 4.56±0.06 | 96.6±0.63 |
| Antimal | 139.0±4.22 | 3.98±0.47 | 95. ±1.63 |
| Chloroquine | 139.4±2.77 | 3.82±0.15 | 98.2±2.06 |
| Coartem | 140.6±3.95 | 4.10±0.35 | 97.8±2.36 |
| Fansidar | 137.6±2.89 | 4.38±0.82 | 95.0±1.99 |
| Malareich | 139.2±2.62 | 3.68±0.24 | 97.6±1.92 |

The results showed that antimal antimalaria drug had no effect on sodium, potassium and chloride concentrations when compared with control 139. ±4.22, 3.98±0.47, 95.0 + 1.63, P>0.05 table 1. Also chloroquine did not affect sodium and chloride concentrations, 139.4±2.7) 98.2+2.06 when compared with control (P>0.05) but decrease potassium concentration as compared with control; 3.82±0.15 (control 4.56±0.06) (P<0.05) was observed, table 1. Coartem drug was observed not to have affected the concentration of sodium, potassium and chloride, 140.6±3.95, 97.8±2.36 (P>0.05) when compared with control table 1.

Also fansidar drug had no significant effect on the concentrations of sodium, potassium and chloride, 137.6±2.89, 4.38±0.82, 95.0±1.63 (P>0.05) when compared with control table 1. Malareich drug had no significant effect on the concentrations of sodium and chloride, 139.2±2.62, 97.6±1.92 (P>0.05) when compared with control. But the drug had a depleting effect on the plasma concentration of potassium, 3.68±0.24 (P<0.05) when compared with control, 4.56±0.06 table 1.

## DISCUSSION

The study has shown the interactions between the different antmalaria drugs with electrolytes in the intracellular and extracellular compartments of the body. Most of the drugs in the study had no effects on the plasma electrolytes e.g fansidar, coartem and antimal, chloroquine and malareich had partial effects, mainly on potassium. This means that such drugs has no harmful effects on the inorganic components of the ICF and ECF so long as the drugs are taken under medical prescription and within the stipulated dosages. This is due to the functions of the electrolytes which may be impaired in wrong medications particularly self medications which is the order of the day.

However, the study has also shown the harmful effects of certain antimalarials taken in adequate dosages. This is seen in the case of malareich and chloroquine which affected the concentration of potassium in the plasma depleting such below the normal range. The effects induced by malareich is quite worrisome as a new preventive antimalaria drug and the rate of its consumption which is high, more so this drug is presumed as alternative for fansidar and chloroquine resistant strain, *Plasmodium falciparum* (Rowland et al, 1979). The physiologic effect is very imperative with respect to certain organs, muscles e.g the heart which pumps blood (Burton 2000). There is therefore the tendency of developing heart failure while on malaeich therapy. There is also the effect of blood stasis due to slow pumping of the heart which can lead to auto clotting and eventual stroke (Oyebola 2002). This effect is very likely as the drug is taken as preventive with slow and cumulative effects. This situation is complicated in malaria disease as malaria itself affects the cardiovascular system by increasing the cardiac output through anaemia and by the destruction of erythrocytes. The disease also directly affect the cardiovascular system as the infected erythrocytes will block the capillary vessels, causing stasis and tissue haemorhage. The hypokalaemia induced by malareich and chloroquine has general physiologic effects on the cells, tissues and organs. In the gastrointestinal system which secretions and persistalsis are purely activities enhanced by the smooth muscle contraction it means such may be impaired and greatly in malaria infection. The impulse generation through membrane and action potentials elicitation by the activity of potassium may be impaired in malareich and chloroquine. The harmful effects of any new antimalaria drug is viewed very seriously particularly the preventive ones. This is because drug pressure is very unlikely in prevention therapy since it in relapse cases i.e. when there is parasitologic and clinical failures in curative therapy that the health seakers move to the next line of drug treatment even without recourse to reseeking the first prescribers consent. In effective preventive therapy therefore malaria disease could be prevented and thus the tendency of spread reduction. This is why the authors are concerned with the development with malareich, however, it is not known if the effect of this drug is due to its tendency of being adulterated. This is because one expected same from antimal and fansidar with same constituents; pyrimethamine/sulphadoxine as malareich. There is therefore need to screen new drugs to see if such drugs are merely old drugs with new names or new drugs indeed.

The mechanism of the depletion of potassium by chloroquine and malareich in this study is not fully understood but it is likely the issue of preferability or preferential competitive binding of these electrolytes by these antimalaria drugs. It could also be a stimulated effects on the plasma proteins by the two drugs to selectively bind potassium as against other electrolytes in concentration. The study also re-emphasizes the roles of antimalarials as models in studying the internal environment as radio isotopes application and radiopharmaceuticals, (Saha, 1998). This is because ordinary it is difficult to assess the ICF directly but antimalarials as labelled radionuclide would unveil internal derailment and information of its homestasis could be easily obtained.

The rising effects from antimalarials now pose a critical question on the policy of drug production and the diseases surveillance. There seems to be less work in the drug production monitoring but more work on the produced ones. This is not a very effective way of controlling malaria as such efforts provide health gap for effective management of the disease. There is need to look into new antimalarials with same active ingredients with old ones using physiologic index to score pharmacologic inputs. Such epidermiologic stride at validating physiologic indices to screen antimalaria drugs will serve many lives from antimalarials scourge which is almost out weighing the malaria scourge.

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