

Hypo and Hyperglycemia; Indicators for Comparative Physiologic Evaluation of Chloroquine, Fansidar, Malareich and Maloxine

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Abstract

Blood glucose levels were determined colorimetrically for 28 (4 weeks) days in thirty five albino rats with the administration of chloroquine, fansidar, malareich and maloxine in comparative doses. Fansidar decreased blood glucose concentration, (43.3 mg/dl) in the first week of the drug administration but a follow up observation of the drug action showed an increase (141.2-135.3 mg/dl) in blood glucose level in the second and third weeks. However, a normal value (82.4 mg/dl) of the blood glucose was obtained in the fourth week of the follow up observation. Chloroquine also exhibited low blood glucose (65.5 mg/dl) in the first week of the administration but normal values were recorded from the second to the fourth week of the follow up. The two new drugs malareich and maloxine maintained normal concentrations of blood glucose throughout the study. It is concluded that fansidar has the tendency of inducing diabetes.

Keywords: New and old antimalarials, hypoglycemia, hyperglycemia.

Introduction

The body needs glucose as energy source for metabolic activities and it can be determined through the circulating amount which is the blood glucose or plasma glucose that is also called blood sugar. Glucose is available as a breakdown product from food eg. carbohydrate, but could also come from the process outside the link carbohydrate called gluconeogenesis particularly during fasting with stored glycogen. The normal level of glucose in a healthy person is 70-120 mg/dl or 3.5-5.0 mmol/l.

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In malaria disease low glucose level e.g. hypoglycaemia indicating a disease situation has been observed (Marsh et al 1995). This is because the malaria parasites require glucose which is lacking in their storage for sustenance (Smyth, 1994). Hypoglycaemia is the result of imbalance between the production of glucose and the quantity for utilization. Chloroquine and fansidar were reported to be linked with hypoglycaemia, (Goyal et al, 1995) but no comparative study has been done with these drugs and the new ones for effective clinical management of malaria disease and complications.

A study was carried by imperative judging of the rate of self medication on antimalaria drugs (Jimmy et al, 2000) without attacks. Chloroquine and fansidar are known curative and preventive antimalarials but not very effective against *Plasmodium falciparum* which is a resistant strain to the drugs. Maloxine and malareich which are curative and preventive drugs are meant as alternative drugs to chloroquine and fansidar. Both drugs are new and particularly malareich as it is very effective against malaria disease. It was therefore necessary to look at the four drugs with respect to their physiologic roles on animals without malaria disease. The major aim was to observe their comparative effects particularly those of the new drugs' as a part of quality assurance to score their safety in application.

Materials and Methods

Thirty five (35) healthy albino rats weighing 0.09 kg – 0.15 kg in average were used for the study. The animals were fed on pellet food and water daily and kept in the Faculty of Pharmacy Animal House University of Uyo throughout the period of study. There is no animal rights in Akwa Ibom State where the study was carried to have obtained consent, however the animals were not injuriously handled. The animals were weighed and divided into four drug groups and the control group. Seven (7) animals were assigned to each drug group and to the control group.

Drug administration

The drugs which based on body weight were prepared and administered according to the methods of Bertram, 2004 and Robert et al 1979. But briefly, the drugs which were prepared by weights of the animals based on the average weight of a man as follows; For the drug group (a) Chloroquine; 4 tablets of 250mg for the first day, 4 tablets for the second and 2 tablets for the third day, dissolved in 100 ml of distilled water and given 1mg/ml to the animals. For the drug group (b) Fansidar, 3 tablets of 525mg were dissolved in 100ml of distilled water and 1mg/ml was given as single dosage. For drug group (c) Maloxine; 3 tablets of 525mg were dissolved in 100ml of distilled water and 1mg/ml was given as single dosage. For drug group (d) malareich, the same dosage as in fansidar and maloxine as it contains the same constituents of sulphadoxine and pyrimethamine in the same concentration; 525mg.

The drugs were administered orally using canula by-passing the oesophagus and delivered into the Stomach, Robert, 1979.

The observation of the effects of the drugs on the blood glucose level was done weekly; 7, 14, 21, and 28 days for a total of 28 days. This was done according to the World Health Organization Standards for monitoring antimalarials on malaria disease (WHO, 1982). However, malaria parasites were not given to the animals and the Schedule was adopted for the drug effects.

At the end of each week, to week four some animals in the groups were anaesthetized with chloroform and sacrificed and blood for glucose analysis was obtained by cardiac puncture. The same procedure was applied for the control group of the animals. The blood samples of 4-5 ml were obtained which varied with the animals and were stored in EDTA anticoagulant bottles and were analysed immediately for glucose levels.

Blood glucose analysis

The blood was centrifuged to obtain the plasma for the glucose analysis. The colorimetric method was applied. 1ml of glucose buffer was added to the test sample and the standard tubes followed by the addition of 0.1ml (10 μ l) of the plasma (test sample) to the tube with glucose buffer and the Standard to the Standard tube sample. The tubes were well mixed and incubated at 27°C for 10 minutes in water bath and the glucose concentrations for the test sample were measured using the wavelength of 520nm. The results were recorded in mg/dl.

Results

The summary of the results is as shown in table 1 and Fig. 1. Fansidar showed a high decrease in blood glucose, (43.3 mg/dl) in the first week of drug administration and high rise (141.2-135.3 mg/dl) in glucose concentration in the second and third weeks of drug action observation period. However, in the fourth week of the observation the glucose level was within the normal range (82.4 mg/dl). With chloroquine low glucose concentration, was recorded also (65.0mg/dl) in the first week of the drug administration but was not as low as that of fansidar. But in the second to fourth week of the drug action observation period normal values of glucose concentration were obtained with the drug. Both malareich and maloxine maintained normal values of glucose concentration for the weeks of the study as shown in Table 1 and Fig. 1.

Table 1. Effect of chloroquine, fansidar, malareich and maloxine on blood glucose level (mg/dl).

Dosage period	Control	Drugs			
		Chloroquine	Fansidar	Malareich	Maloxine
Week1	100.0	65.0	43.3	91.2	72.6
Week2	105.9	111.8	141.2	117.6	100.0
Week3	107.4	120.4	135.3	119.1	100.1
Week4	91.2	111.8	82.4	70.6	76.5

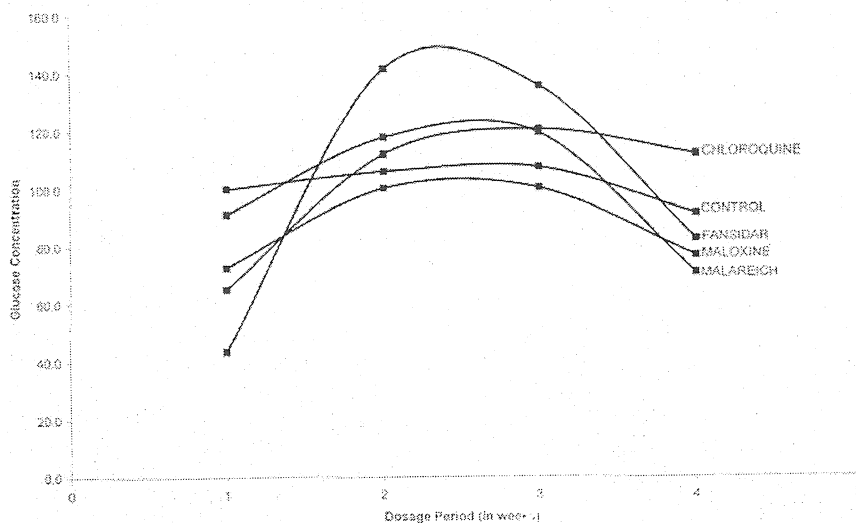


Figure 1. Effect of Chloroquine, Fansidar, Malareich and Maloxine on blood glucose level (mg/dl)

Discussion

The results in this study reflect an unsteady concentration of blood glucose in the plasma of the animals after the administration of the different forms of antimalaria drugs. For instance, fansidar in the first week a lower variation from the normal value of blood glucose which is 70 – 120 mg/dl, indicating hypoglycaemia. In the second and third week of the drug action observation period high glucose levels were elicited by the drug, indicating hyperglycaemia. However, the low glucose

level was in line with previous studies. The new observation with our study was the occurrence of hyperglycaemia discovered due to our follow up pattern studies, which could be a feedback response by insulin to increase the glucose level. The implications of the observation are rather noteworthy. First, fansidar is taken as a preventive drug in malaria disease and majority of the consumers are on self medication, (Jimmy et al 2000).

Under these circumstances the damage is high in respect to the tendency to evoke a decrease in blood glucose level.

Moreover the parasite clearance rate with fansidar treatment after the parasites have established in the blood stream is quite low and there is the tendency to repeat the drug when there is the treatment failure. This would fluctuate the blood glucose level more hence causing danger of hyperglycaemia and hypoglycaemia. The hyperglycaemia observed in the study is an indication that fansidar may induce diabetic condition in a normal condition. Diabetics is a more deadly disease than malaria though malaria kills faster than diabetes but a diabetic may not be cured. Diabetic patients may also be in danger of using fansidar as malaria regimen both as preventive and curative. However, a more elaborate study would be necessary to assess the role(s) of fansidar in diabetic complications and as a therapy for diabetes. Hyperglycaemia in our study with chloroquine is in line with previous observations, (Goyal, 1995). But the value of the glucose was not as low as that of fansidar indicating the safety of chloroquine though both drugs are not very potent against the resistant strain; *Plasmodium falciparum*, (Knowles, 1984, Doberstyn, 1976).

The two new drugs; maloxine and malareich have shown physiologic normalcy in the study. Since both drugs contain sulphadoxine, pyrimethamine in equal concentration (525 mg) with fansidar, one would have expected the same effect as in fansidar.

However, the hyperglycaemia observed in our study needs further studies.

Perhaps more concise evaluation of the true ingredients of all the rebranded versions of the new antimalaria drugs need be done to assess safety status. But in our study, maloxine and malareich had no adverse effects on the blood glucose level. However, this is not to certify the drugs as very safe since only glucose level could not summarize the overall physiologic evaluation of the drugs but as an aspect of such. This is why such evaluations are necessary as a continuing process at this period of many new drugs with increasing pressure with the tendency of acquiring better clinical management of malaria disease.

The use of antimalaria drugs on animals without malaria parasite in our study was to emphasize comparative assays of new and old drugs particularly with those drugs often taken as preventive against malaria. It is seen from our study that fansidar and chloroquine taken in malaria situation will aggravate hypoglycaemic and hyperglycaemic situation as malaria itself induces hypoglycaemia (Marsh et al. 1995) making more complications. A good logistic approach is thus necessary particularly involving public enlightenment and self medication and intensive studies on old and new antimalaria drugs and not just intensive drugs production.

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