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Reducing Side Effects of Chloroquine with *Medicinal Synthetic Aluminum-Magnesium Silicate*® [Msams: $Al_4(SiO_4)_3 + 3Mg_2SiO_4 \rightarrow 2Al_2Mg_3(SiO_4)_3$] before Assessing Its Anti-Covid-19 Efficacy

Maduike Ezeibe[1*], Favour Onyeachonam[1], Ijeoma Ogbonna[1], Clara Akpan[1], Mary Sanda[1], Ekenma Kalu[1], Njoku Njoku[1], Munachi Udobi[1], Ugochukwu Agu[2]

[1]College of Veterinary Medicine, M'ichael Okpara University of Agriculture, Umudike, Nigeria
[2]Directorate of Information Computer Technology, Michael Okpara University of Agriculture, Umudike, Nigeria
Email: *maduikeezeibe@yahoo.com

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Abstract

To reduce Chloroquine's (CQ) side effects, so that increasing its duration for anti-*Covid*-19 trials could be safe, the drug was potentiated by stabilizing it with Medicinal synthetic Aluminum-magnesium silicate (MSAMS). CQ-treatment for five *Plasmodium berghie*-infected mice-groups were: 7 mg/kg (normal dose); 7 mg/kg (CQ-MSAMS); 7 mg/kg (CQ-MSAMS + B-vitamins), 5.25 mg/kg (CQ-MSAMS + B-vitamins) and the control. Means of parasitaemia, 42.00 ± 15.74 of the normal-dose group, 37.22 ± 11.88 of the 7 mg/kg (CQ-MSAMS) group and 33.57 ± 12.62 of the 7 mg/kg (CQ-MSAMS + B-vitamins) group showed no significant ($P \geq 0.05$) reduction from 52.50 ± 11.99 of the control, but the 5.25 mg/kg (CQ-MSAMS + B-vitamins) dose, cleared ($P \leq 0.01$) the parasiteamia (00.00 ± 00.00), showing that MSAMS-potentiated Chloroquine, has best efficacy at 75% of the recommended dose. Fever and anemia were absent at that 5.25 mg/kg, suggesting that lower doses of CQ have reduced side effects.

Keywords

Antiviral Treatment with Chloroquine, Lower Doses, Reduction of Side Effects, MSAMS

1. Introduction

Duration of treatment for malaria with Chloroquine is only five days. Despite

this short duration, Chloroquine has been banned in most countries, mainly because of its intolerable side effects. Yet as a response to ongoing Covid-19 pandemic, there are suggestions to test it for anti-Covid-19 efficacy. Treatment of viral diseases requires durations, longer than five days. Use of Chloroquine, for antiviral trial, at its present dose, could worsen its toxicity and mare any benefit it may have in the treatment of Covid-19. Therefore, there is need to reduce dose of the drug that would achieve desired effects both for its trial as anti-Covid-19 medicine and to restore its anti-malaria efficacy.

Malaria is caused by a protozoan of the genus *Plasmodium* [1]-[6]. The disease has afflicted man for over 50,000 years and the parasite, *Plasmodium* is reported to have been a human pathogen for entire history of the species.

The disease is wide spread in tropical and subtropical regions. It is presently endemic around the equator, including parts of America, Asia and Africa. However, it is in sub Saharan Africa that 85% - 90% of malaria fatalities occur [7]. Each year, there are approximately between 350 and 500 million cases of malaria, killing between one and three million people in sub Saharan Africa. Majority of malaria fatalities are among young children, under five years of age and pregnant women. Ninety percent of malaria-related deaths occur in sub Saharan Africa and most of the infections imported into Europe also come from tropical Africa. Malaria cases in Africa account for approximately 90% of the disease in the world.

Most mammalian malaria cases were treatable with Chloroquine [8] [9] at a dosage of 7 mg/kg for 5 days (35 mg/kg body weight). The drug could be given as an intramuscular injection or per os. The bitter taste of Chloroquine precludes putting it in food for animals. For its inexpensiveness, Chloroquine was, for many decades, drug of choice in mass treatment of Malaria in endemic rejoins. This has led to emergence and spread of generations of *Plasmodium* strains *(*especially *P. falciparum*) that are resistant to the drug. So, there is need to search for drugs to be combined with Chloroquine in order to restore its efficacy. It is also, important to find a treatment-strategy that would reduce its toxicity (side effect).

The three dimensional colloidal structures which platelets of molecules of Aluminum-magnesium Silicate (AMS) form when in solution have ability to stabilize drugs [10]. To stabilize means to protect against destruction. This prolongs time of high bioavailability of drugs that are in formulations with AMS so that their effects improve. Also, AMS is made of platelets that are only 0.96 nm thick [10]. So, it is made of *Nanoparticles*. *Nanoparticles* enhance delivery of drugs across physiological barriers. That means that the AMS may in addition to prolonging time of high bioavailability of Chloroquine, enhance its delivery to targets, including across blood brain barrier. That may lead to better treatment of malaria including cerebral malaria. Also both Chloroquine and AMS have been reported to have antiviral effects [11] [12]. So, a formulation of Chloroquine and AMS may have synergistic antiviral effect.

To test effects of a medicinal synthetic Aluminum-magnesium silicate (MSAMS) on side effect of Chloroquine and on its anti-malaria efficacy, albino mice were used for experimental treatment at two Chloroquine dose levels (7 mg/kg and 5.25 mg/kg).

2. Materials and Methods

Fifteen adult mice of mixed sexes, which weighed approximately 0.03 kg, each were randomly assigned into five groups, each of three mice and infected by intra-peritoneal (IP) inoculation of 1 ml of blood of donor mouse which contained 2×10^8 *Plasmodium berghei* parasitized RBCs per ml (diluted in normal saline).

Three of the groups were treated, with: 7 mg/kg, Chloroquine alone; 7 mg/kg Chloroquine and 50 mg/Kg MSAMS; 7 mg/kg Chloroquine and 50 mg/kg MSAMS plus 0.I ml of B-vitamins, respectively. The fourth group was treated at 75% of normal dose of Chloroquine (5.25 mg/kg) and 75% of normal dose of MSAMS (37.55 mg/kg) plus, 0. I ml of B-vitamins while the fifth group served as control.

The two Chloroquine formulations were reconstituted in water, such that each mouse was drenched same volume (0.1 ml) to deliver the required dose for the group (7 mg/kg or 5.25 mg/kg):

$$\text{Quantity}\left(\text{Q}\right)\text{ of drug formulation needed for a mouse} = \frac{\text{Dose}\left(D\right)\times\text{Weight}\left(W\right)}{\text{Concentration}\left(C\right)}$$

1) For the 100% Chloroquine formulation at 7 mg/kg(CQ):

C = 100 g CQ in 100 g = 100,000 mg/100g = 1000 mg/g

Since mean weight of a mouse is 0.03 kg, for dose of 7 mg/kg

$$\frac{7\text{ mg}}{\text{kg}}\times\frac{0.03\text{ kg}}{1}\times\frac{\text{g}}{1000\text{ mg}} = 0.00021\text{ g}$$

To get a measurable weight of the drug formulation (0.1 g), number of mice that would require 0.1 g was calculated to be 500.

To give each mouse 0.1 ml, the 0.1 g was dissolved into 50 ml solution (49.9 ml of water + 0.1 g of CQ = 50 ml, enough for 500 mice).

2) For the CQ-MSAMS drug formulation (20% CQ) at 7 mg/kg:

Volume of solution for 0.1 g was calculated as = $50\text{ ml}\times\frac{20}{100} = 10\text{ ml}$ (9.9 ml of water + 0.1 g of CQ = 10 ml, enough for 100 mice)

3) For the CQ-MSAMS drug formulation (20% CQ) at 5.25 mg/kg (75% of 7 mg/kg)

Volume of solution for 0.1 g was calculated as = $10\text{ ml}\times\frac{100}{75} = 13.3\text{ ml}$ (13.2 ml of water + 0.1 g of CQ = 13.3 ml, enough for 133 mice).

For each of the treated groups, treatment was initiated, 10 days post infection (PI) and lasted for 7 days. *Plamodium berghei* parasitaemia, packed cell volume of blood, hemoglobin concentration, total red blood cells counts and body tem-

perature of the five groups of mice were tested for, on days: 1, 7, 14 and 21 post treatment (PT). Means of: parasitaemia, packed cell volume, haemoglobin concentration, total red blood cell counts and body temperature for the different groups were compared for statistical differences by Analysis of Variance (ANOVA). All through the experiment, the mice were humanely treated according to ethical standards laid down in the 1964 Declaration of Helsinki, as, operational in Nigeria.

3. Results

Parasitaemia (%): Mean parasitaemia, 42.00 ± 15.74, 37.22 ± 11.88 and 33.57 ± 12.62 of three of the treated groups (7 mg/kg CQ alone, 7 mg/kg CQ-MSAMS and 7 mg/kg CQ-MSAMS plus B-Vitamins) did not vary ($P \geq 0.05$) from 52.50 ± 11.99 of the untreated group but mean parasitaemia (00.00 ± 00.00) of the group treated with 75% of normal dose of Chloroquine (5.25 mg/kg) stabilized in MSAMS plus B-vitamins was significantly ($P \leq 0.01$) lower than parasitaemia of both the untreated group and of the other treated groups (Table 1).

Packed cell volumes (PCV): PCV, 37.64 ± 2.55 of the group treated with normal dose of Chloroquine (7 mg/kg) did not vary (≥0.05) from 41.00 ± 6.00 of the untreated group or from 35.89 ± 3.74, 41.75 ± 5.57 and 37.40 ± 5.25 of the groups treated with 7 mg/kg of Chloroquine in MSAMS, 7 mg/kg of MSAMS-Chloroquine drug formulation and vitamins and 5.25 MSAMS-Chloroquine drug formulation and vitamins respectively (Table 2).

Haemoglobin concentration (Hb): Means of Hb, 12.55 ± 0.85, 11.97 ± 1.25, 15.18 ± 1.39, 13.47 ± 1.69 and 13.70 ± 2.00 of the groups of mice treated with 7 mg/kg, Chloroquine, 7 mg/kg Chloroquine in MSAMS, 7 mg/kg Chloroquine in

Table 1. *Plasmodium berghei* parasitaemia (%) in mice treated with Chloroquine phosphate stabilized with the *Medicinal synthetic Aluminum-magnesium silicate* and with B-vitamins.

	7 mg/kg		5.25 mg/kg		Control
	CQ	CQ-AMS	CQ-AMS + Vit	CQ-AMS + Vit	
	150	90	45	0	80
	60	80	0	0	30
	10	0	0	0	35
	68	35	70	0	65
	30	40	0	0	-
	0	0	75	0	-
	40	20	45	0	-
	20	70	-	0	-
	0	0	-	0	-
Mean	42.00 ± 15.74^{ab}	37.22 ± 11.88^{ab}	33.57 ± 12.62^{ab}	0.00 ± 0.00^{a}	52.50 ± 11.99^{b}

Different superscripts in a row indicate significant differences between the means at the level of probability: $P \leq 0.05$.

MSAMS and with vitamins, 5.25 mg/kg Chloroquine in AMS and vitamins and the control respectively, were not significantly ($P \geq 0.05$) different (Table 3).

Red blood cell counts: Means of RBC of groups of mice treated with Chloroquine at dose of: 7 mg/kg (46.71 ± 3.41), 7 mg/kg with MSAMS-Chloroquine

Table 2. Packed cell volume (%) of *Plasmodium berghei*-infected mice treated with Chloroquine phosphate stabilized with the *Medicinal synthetic Aluminum-magnesium silicate* and with B-vitamins.

	7 mg/kg		5.25 mg/kg		Control
	CQ	CQ-AMS	CQ-AMS + Vit	CQ-AMS + Vit	
	20	26	22	16	35
	26	32	40	20	47
	40	22	49	16	-
	39	48	14	20	-
	35	35	55	52	-
	45	25	45	45	-
	43	52	57	49	-
	38	34	52	52	-
	35	49	-	54	
	45	-	-	50	-
	48	-	-	-	
Mean	37.64 ± 2.55[a]	35.89 ± 3.74[a]	41.75 ± 5.57[a]	37.40 ± 5.25[a]	41.00 ± 6.00[a]

Different superscripts in a row indicate significant differences between the means at the level of probability: $P \leq 0.05$.

Table 3. Hemoglobin concentration (g/100ml) of *Plasmodium berghei*-infected mice treated with Chloroquine phosphate stabilized with the *Medicinal synthetic Aluminum-magnesium silicate* and with B-vitamins.

	7 mg/kg		5.25 mg/kg		Control
	CQ	CQ-AMS	CQ-AMS + Vit	CQ-AMS + Vit	
	6.70	8.60	7.30	5.40	11.70
	8.60	10.70	14.30	6.70	15.70
	13.30	7.30	16.30	5.40	-
	13.00	16.00	13.90	16.70	-
	11.70	11.70	18.30	17.30	-
	15.00	8.30	15.90	15.00	-
	14.30	17.30	19.00	16.00	-
	12.70	11.40	17.30	17.40	-
	11.70	16.40	-	18.10	-
	15.10	-	-	16.70	-
	16.00	-	-	-	-
Mean	12.55 ± 0.85[a]	11.97 ± 1.25[a]	15.18 ± 1.30[a]	13.47 ± 1.69[a]	13.70 ± 2.00[a]

drug formulation (45.50 ± 4.24), 5.25 mg/kg with MSAMS-Chloroquine drug formulation and vitamins (45.65 ± 3.63) and of the untreated group (44.00 ± 3.08) did not vary ($P \geq 0.05$) but RBC, 59.28 ± 3.14 of the group treated with 7 mg/kg of the MSAMS-Chloroquine drug formulation and vitamins was significantly ($P \leq 0.05$) higher than mean RBC counts of the other groups (Table 4).

Rectal temperature: Means of rectal temperature: 38.07 ± 0.37, 37.62 ± 0.49, 38.58 ± 0.25, 38.33 ± 0.40 and 37.80 ± 0.20 of the groups of mice treated with 7 mg/kg, Chloroquine, 7 mg/kg Chloroquine in MSAMS, 7 mg/kg Chloroquine in MSAMS and vitamins, 5.25 mg/kg Chloroquine in MSAMS and vitamins and the control respectively, were not significantly ($P \geq 0.05$) different (Table 5).

Table 4. Red blood cell counts (×10,000) of *Plasmodium berghei*-infected mice treated with Chloroquine phosphate stabilized with the *Medicinal synthetic Aluminum-magnesium silicate* and with B-vitamins.

	7 mg/kg			5.25 mg/kg	Control
	CQ	CQ-AMS	CQ-AMS + Vit	CQ-AMS + Vit	
	37.00	45.60	50.00	36.00	35.00
	44.40	52.40	65.00	38.00	46.60
	43.00	38.00	62.50	40.00	45.50
	55.00	33.60	50.00	47.00	48.90
	48.00	32.00	68.30	33.00	-
	32.00	67.70	59.90	40.00	-
	63.00	42.00	-	65.00	-
	58.00	36.50	-	59.00	-
	40.00	62.20	-	38.50	-
	-	-	-	60.00	-
Mean	46.71 ± 3.41[a]	45.56 ± 4.24[a]	59.28 ± 3.14[b]	47.65 ± 3.63[a]	44.00 ± 3.08[a]

Table 5. Body temperature ((˚C)) of *plasmodium berghei*-infected mice treated with Chloroquine phosphate stabilized with the *Medicinal synthetic Aluminum-magnesium silicate* and with B-vitamins.

	7 mg/kg			5.25 mg/kg	Control
	CQ	CQ-AMS	CQ-AMS + Vit	CQ-AMS + Vit	
	38.50	38.80	38.70	38.80	38.00
	39.00	37.90	39.20	39.10	37.60
	38.30	37.80	38.00	37.30	-
	36.20	35.80	38.40	36.90	-
	38.20	37.80	-	39.00	-
	38.20	-	-	38.90	-
Mean	38.07 ± 0.39[a]	37.62 ± 0.49[a]	38.58 ± 0.25[a]	38.33 ± 0.40[a]	37.80 ± 0.20[a]

Different superscripts in a row indicate significant differences between the means at the level of probability: $P \leq 0.05$.

4. Discussion

There was no statistical difference between *Plamodium berghei* parasitaemia in mice treated with normal dose of Chloroquine (7 mg/kg) and in the control group. When Chloroquine was stabilized with the MSAMS the parasitaemia reduced, though slightly. It has been reported that MSAMS is a stabilizing agent. To stabilize means to protect from destruction, the results therefore suggest that MSAMS may have stabilized Chloroquine to prolong time it remains at high bioavailability and so improved its efficacy. When the same 7 mg/kg Chloroquine stabilized in the MSAMS was used in synergy with B-vitamins to treat the mice, the paraitaemia reduced further and total red blood cell count was significantly increased, suggesting reduction in level of anemia. However, when dose of Chloroquine was reduced to 75% of its recommended dose (5.25 mg/kg) and it was stabilized with the MSAMS and used in synergy with B-vitamins, the parasitaemia was completely cleared. It has also been reported that prolonging time of high bioavailability enhances antimicrobial activities of drugs [13].

The finding that when antimicrobial medicines are stabilized with the Medicinal synthetic Aluminum-magnesium silicate, their best therapeutic effects are obtained with 75% (not 100%) of their recommended doses, has been consistent with all the medicines so far tested. The treatment-strategy improved anti-protozoal and antibacterial efficacies of Suphadimidine, anthelminthic efficacy of Piparazine and antibacterial efficacies of Ampicillin and Cotrimoxazole [14]-[19].

AMS is also a zeolite and zeolites are reported to deliver drugs to desired targets. So, both prolongation of time of high bioavailabilty of Chloroquine and delivery of the drug to targets may be responsible for the improved effects the AMS-stabilized Chloroquine had on the plasmodia infection.

Chloroquine has been reported to have no effect on malaria parasites in the liver and those in other organs and tissues [16]. It acts only on parasites in the blood. The drug is also reported to have toxic effects and its toxicity leads to both immune suppression and iron deficiency anemia [20] [21]. Once level of any anti-malarial drug used in treatment, reduces in blood of treated animals, malaria parasites in liver, spleen and lungs return to blood circulation. It is possible that parasites that returned to blood circulation from organs, were responsible for the high parasiteamia recorded in the groups treated with Chloroquine at dose of 7 mg/kg. The lower dose of Chloroquine used may have minimized its toxic effects while stabilizing it with the MSAMS improved its anti-plasmodia effect.

Also, the B-vitamins are immune stimulants. Vitamins B_1 (Thiamine) and B_5 (Pantothenic acid) combine with phosphate compounds to form coenzymes which are involved in formation of acetyl coenzyme A, an important intermediate in cell respiration. Vitamin B_2 (Riboflavine) combines with certain phosphate compounds to form flavine adenine dinucleotide (FAD) which is an important coenzyme, concerned with transport of hydrogen atoms in cell respira-

tion. Vitamin B_6 (Nicotinic Acid) forms coenzymes, Nicotinamide adenine dinucleotide (NAD) and Nicotinamide adenine dinucleotide phosphate, required as hydrogen acceptors in cell respiration. Vitamin B_{12} (Cobalamin) is required for formation of red blood cells.

So, synergy between minimized side effects of Chloroquine by reducing its dosage, enhanced immune response of the mice by the B-vitamins and improved anti-plasmodia effect of the Chloroquine by the MSAMS may be responsible for the complete elimination of *P. berghei* infection recorded in the group treated at dose of 5.25 mg/kg with Chloroquine stabilized in the MSAMS and with B-vitamins.

That there was no significant difference between PCV, Hb, RBC and body temperature of the control group and those of the treated groups agrees with the report, that plasmodium infection in rats and mice do not produce serious clinical disease [22].

Results of this study show that Chloroquine reduced parasitaemia in all the treated groups but in an earlier trial of the MSAMS on Chloroquine [23], mice treated with normal dose of Chloroquine had higher parasitaemia than untreated mice. That finding was then suggested to be due to Chloroquine toxicity, because Chloroquine is known to inhibit uptake of iron and to destroy plasmodium-infected Rbcs. Chloroquine toxicity is also known to result in immune-suppression and the drug has no effect on parasites that migrate to tissues. So, plasmodia parasites in tissues that return to blood of animals that are immune-suppressed could multiply rapidly to lead to high parasitaemia. We suggested that the high parasitaemia in the group treated with 7 mg/kg Chloroquine was due to Chloroquine toxicity. Also, in that earlier experiment, there was no mortality in the group of untreated mice while mortalities were recorded in two groups treated at Chloroquine dose of 7 mg/kg. That was also attributed to Chloroquine toxicity. Results of present study do not support the claim that Chloroquine toxicity is as prominent as was earlier suggested. The *P. berghei* isolate used in that earlier study may have been more resistant to Chloroquine than the generic resistance the parasite has developed against the drug. So, side effects of Chloroquine may have manifested while its antiplasmodial effects were resisted.

Researchers had suggested need to search for drugs to combine with Chloroquine [9] to improve its effects because its use in mass treatment of malaria has led to emergence of resistant plasmodia strains, especially those of *Plasmodium falciparum*.

From results of this study, stabilizing drugs with MSAMS, minimizing side effects of the drugs by using 75% of their recommended doses and administering immune-stimulants to treated patients appear to be effective strategies to restore Chloroquine's anti-malaria efficacy. Also, **Ismercquine®** [24], a formulation of MSAMS (broad spectrum antiviral medicine and anti retroviral medicine) [25] and Chloroquine (a suggested antiviral medicine, with its side effects reduced)

may have better anti-Covid-19 efficacy than MSAMS alone or Chloroquine alone.

Authors' Contributions

The authors collaborated for the research. Author, ME designed the experiments and drafted the manuscript. Authors IO, CA, MS, EK, NUN, MU and UA *analyzed the data* while author FO processed the manuscript for publication. All the authors read the draft-manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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