Add DR #10

Bio-Normalizer (BN) Treatment Out-Come of Uncomplicated Malaria in National Capital District, Papua New Guinea.

1. J.K. Wangi; 2. J.A. Venudi; 3. P. Auharai.

1. Medical Doctor – National Epidemiologist / Director Disease Control, National Department of Health, P.O. Box 807, Waigani, Papua New Guinea.
2. Managing Director, Bio-Normalizer, PNG LTD, P.O. Box 83, University, National Capital District, Papua New Guinea.
3. Senior Nursing Sister, National Capital District Health Services, National Capital District, Papua New Guinea.

Bio-Normalizer (BN) Treatment Out-Come of Uncomplicated Malaria in National Capital District Papua New Guinea.

1.J.K. Wangi; 2. J.A.Venudi, 3.P.Auhari.

1. Medical Doctor-National Epidemiologist/Director Disease Control , National Department of Health, P.O. Box 807, Waigani; PNG.
2. Managing Director Bio-Normalizer, PNG Ltd; National Capital District Papua New Guinea.
3. Senior Nursing Sister, National Capital District Health Services; NCD; Papua New Guinea

Abstract

Bio-Normalizer an all natural food manufactured by Sun-O International, Inc Japan from fermenting Philippines papaya has promising properties for the treatment of multitude of medical conditions. This product had gained entry into Papua New Guinea almost 18 –24 months prior to this study and was rapidly becoming popular with the public country wide in the treatment of various medical conditions including malaria. This has made it necessary to conduct this study to ensure that the product is efficacious and safe for public use in the treatment of malaria. So this study was conducted in 2002-2003 in the National Capital District of PNG, to document the treatment outcome of the product . The study was a 5day invivo study (clinical study). Of the 40 study participants initially selected, 11 were excluded due to loss to follow up and 29 were treated and followed up daily for 4 days. During daily follow up supervised treatment with BN was given with the collection of blood slides for malaria microscopy. Of the 29 patients, 23 (79.3%) had an adequate clinical response (ACR). Symptomatic relief with corresponding drop in parasitaemia was observed to be dramatic within the first 24 hours of treatment with the product. No side effects were documented with the use of this product. No early treatment

failures were observed. Stratified analysis according to gender, age of the study

participants and parasite types were conducted on treatment outcome and it was found that the outcomes were similar in these stratums. On the basis of these results it has been concluded that BN is efficacious and safe in the treatment of malaria caused by Plasmodium falciparum and the other malaria parasites in the National Capital District and Papua New Guinea. The study also recommended for further studies to document resistant and recrudescence patterns with the use of this product and also to assess the long term effect on the immunity status of persons treated with the product.

Introduction

Bio-Normalizer (BN) has promising properties for the treatment of multitude of medical conditions and has been in use in many countries with excellent results .It is an all natural food manufactured by Sun-O International , Inc; Japan from fermenting Philippine papaya.

It has three major benefits to human body. First for its anti-aging potential, principally by inhibiting the increase of acid substances and preventing the accumulation of free radicals and age-inducing elements. Second as an immuno-modulator that strengthens the immune system in the fight against potentially harmful viruses and other organism. Thirdly as a metal –ion chelator (helps in eliminating harmful heavy metals from the body otherwise not eliminated by normal elimination) as a regulator of free radicals in the body that promotes healthy DNA and thus, a disease free body.

The product was introduced by a private company on commercial basis some 18-24 months ago in the country and the public were buying and using it to treat malaria and many other medical conditions and were experiencing fast relieves and even cures without any side effects.

Following this the founder of the product, Professor James Osato of Sun-O International and a team of company Officials visited the Secretary of Health in mid 2003 and discussed the possibility of introducing the product for routine use by the Department of Health and others in the

country. The Health Department was interested in the product, however recommended for clinical studies to document its efficacy and safety before further considerations can be entertained .

The aim of this study was to take a quick look at the outcome or efficacy of treating malaria cases with Bio-Normalizer as a possible alternative agent of malaria treatment in Papua New Guinea.

The study objectives were to determine the practical efficacy of BN in clearing the malaria parasite in the blood , reducing fear and other symptoms of malaria, and in effecting a cure and to record any side effects associated with its use.

Test System:

The study consisted of recording essential patient information like age, sex, clinical assessment of traditional symptoms of malaria (fever, headache, body pains), and the presence of other febrile conditions, doing blood slides for malaria parasites, administering supervised treatment with BN on Day 0 which is the pre-treatment day. Following this follow ups were made and study subjects were given supervised BN treatment and blood slides taken for Days 1 to 4.No temperature readings or hematological tests were carried out. For children information was obtained through interviewing them directly (for children 13 years or older) or through their parents or guardians. Before the performance of clinical trial patients underwent a pretreatment clinical examination. Patients meeting all inclusion criteria and showed no danger signs (see below) and had informed consent obtained from them or their parents/guardians , were recruited for the study.

Danger Signs:

- Not able to drink or breast feed
- Vomiting everything
- Recent history of convulsions
- Lethargic or unconscious state
- Unable to sit or stand.
- Other obvious febrile medical conditions

Inclusion Criteria:

- New case - fever in the last 24 to 72 hours with no treatment. No differentiation was made for P.Falciparum malaria and others. This was done in the analysis.
- Absence of danger signs
- Absence of history of hypersensitivity to any drugs
- Absence of febrile conditions caused by diseases other than malaria
- Agreement to come for follow up and repeat blood test and treatment with BN for four (4) days.
- Informed consent from patients or parents and guardians.

Exclusion Criteria:

- No informed consent
- Showing of one or more danger signs
- Treated for malaria in last two weeks
- Presence of any other febrile conditions
- Treatment failure

Classification of Therapeutic Response:

Three categories of therapeutic response as recommended by the World Health Organization , namely Early Treatment Failure (ETF), Late Treatment Failure (LTF), and Adequate Clinical Response (ACR) were used to categorize clinical response to the agent. These are as defined below:

Early Treatment Failure:

If the patient develops one of the following conditions during the first three days of follow up (day1 to day 4. Development of danger signs or severe malaria on days 1, 2, or 3 in the presence of parasitaemia. Fever of greater than or equal to 37.5 C on day 2 with parasitaemia > of day 0 or pre-treatment reading. Fever of greater than or equal to 37.5 C on Day 3 and parasitaemia greater than or equal to 25% of the count of day 0.

Late Treatment Failure:

If the patient develops one of the following conditions during follow-up period from Day 4 to 14. Parasitaemia on day 3 <25% of day 0 count and development of danger signs or severe malaria on any day from day 4 to Day 14 in the presence of parasitaemia . Parasitaemia on day 3<25% of the

count on day 0 and fever greater than equal to 37.5 C in the presence of parasitaemia on any day from Day 4-Day14.

Adequate Clinical Response:

If the patients shows the following during follow-up period ie up to 14 days. Parasitaemia on day 3 <25% of Day 0 and no parasitaemia on day 4

Parasitaemia on day 3 <25% of count of Day 0 and no parasitaemia on Day 14.

Parasitaemia on Day 3 < 25% of count of day 0 and parasites present on day 14 and temperature of <37.5 C.

It is to be noted that this study did not strictly follow the definitions of the three categories of response because the purpose of it is to take a quick look at the effect of this agent to form the basis of a proper study in future. So the follow up period have been limited to only 4 days.

Clinical Cure:

Absence of parasitaemia and fever and headache.

Alternative treatment for Drug failure :

The indication for alternative treatment at any time between day 0 and day4 was built into the study with the aim of avoiding aggrevation of clinical condition and risk to the patient . These indications include those of early and late treatment failure as mentioned above. The alternative treatment designated was the treatment regime currently used in the country consisting of combination treatment of Chloroquine and Fansidar for uncomplicated malaria and Arthemeter and Fansidar for complicated malaria.

Removal Criteria:

Failure to complete treatment or follow up and or occurance of one or more of danger signs or of any concomitant disease that would interfere with classification of treatment outcome

Method:

Study Type: Five days invivo study .

Reference Population : Population of Papua New Guinea

Experimental Population : Indigenous Papua New Guinea patients presenting with symptoms of malaria -fever, headache and body pains with or without positive blood test for malaria.

Study Population : New patients presenting with symptoms of malaria (as above) and who have not received any anti-malaria treatment prior to enrollment in the study, attending public urban clinics or who reside in the National Capital District of Papua New Guinea at the time of the study.

Eligible population : Forty (40) individuals with fever and head ache and body pains

Willing population : A sample size of 29 individuals were selected using convenient sampling technique for the study.

Process : The study subjects were identified by trained health workers and research assistants using standard screening procedures with the application of inclusion and exclusion criteria applied The purposes of the study was explained to the study participants and informed verbal consents were obtained from each study participants or their parents or guardians. A structured questionnaire containing information on age, sex, symptoms, blood test results, and malaria parasite species type, treatment status and side effects were administered to the participants.

The study participants were given supervised treatment (Adult –4 tablets and children tablets given according to weight) on day 0 and advised not to take any other treatments for the next four days. They were also advised to report any bad effects they felt when getting the agent or also if their symptoms were not getting better or if they had taken any other drugs during the follow up period. The patients were followed up in their houses and given supervised daily treatment for four days. With the exception of parasite species, all the information as per questionnaire and blood slides were collected on each day for the five days. Blood slides were taken by senior health worker for each study participant on pre-treatment day and on every day for 4 days . Blood slide microcopy was performed by a senior medical laboratory technician.

Data Analysis:

Computer software – EpiInfo 2000 was used for data management and analysis and Microsoft Excel was used to generate the graphs.

General Descriptive analysis and stratified analysis according to age, sex and parasite types were carried out for the study parameters. This was necessary because the response to the agent could vary according to the level of immunity and parasite type in the patient (5).

Results

A total of 40 study participants were involved in the study. Of these only 29 met the inclusion criteria and 11 were excluded from the study for failure to complete treatment or follow up. Pre-treatment clinical examination showed no other obvious causes of fever.

Of the 29 eligible and willing study subjects had blood slides done and 16 (55.1%) had blood slide positive and 12 (41.4%) had negative blood for malaria parasites. Of the 16 blood slide positive cases, 10 (%) were Plasmodium falciparum malaria and 5 (%) were Plasmodium vivax malaria . Of the 15 P.Falciparum malaria all trophozoites or sexual form of parasite and the 1 P.vivax was also in trophozoite form. From pre-treatment examination, 13/16, or 81.3% (95% CI 54.4%-96%), had fever, 15/16 or 93.8% (95% CI, 69.8%-99.8%) had fever and all 16/16 (100%) of them had headache.

Of the 29 who completed the study there were no evidence of early or late treatment failure. No other adverse effects were observed. None of the study subject had to be given alternative treatment.

Of this 21 (72%) were adults, 5 (17%) were children, and 3 (10%) had no information on their ages. Eight (28%) of the participants were . Females, 18 (62 %) were males and 3 had ambiquous information on their gender.

Table 1.0 shows symptoms of malaria and blood test results and days of treatment and follow up.

Table 1: Bio-Normalizer Treatment Outcome of Uncomplicated Malaria Patients in the National Capital District , Papua New Guinea, 2002-2003.

	Days of Follow Up and Treatment				
	0	1	2	3	4
Symptoms Present					
Fever	27/29 (93.3%)	6/29(20.7%)	1/29(3.4%)	1/29(3.4%)	1/29 (3.4%)
Headache	26/29(89.7%)	4/29(13.8%)	2/29(6.7%)	0/29(0%)	0/29(0%)
Body pains	23/29(79.3%)	2/29(6.7%)	1/29(3.4%)	1/29(3.4%)	0/29(0%)
Positive blood test results	16/29(55.2%)	5/29(17.2%)	2/29(6.7%)	0/29(0%)	0/29(0%)

The table 1, shows that fever was the predominant symptom (93%) followed by headache (90%) and body pains (79%). Pre-treatment blood test positivity rate is 52%. In Day 1 there was reduction of fever by over 72% of the study subjects, headache by over 65% and body pains by over 86% and blood test positivity by 38%. Full parasite clearance was achieved in Day 3 of follow up or after 4 days of treatment, with corresponding clearance of headache. By day 4 of follow up parasite clearance was maintained and body pains was cleared as well. Fever persisted in over 3% of the study subjects . No statistical significance was observed in these results.

Table 2: Bio-Normalizer Treatment Outcome of Adult Uncomplicated Malaria Patients in the National Capital District , Papua New Guinea, 2002-2003.

	Days of Follow Up and Treatment				
	0	1	2	3	4
Symptoms Present					
Fever	18/21(85.7%)	4/21(19%)	1/21(4.8%)	0/21(0%)	0/21(0%)
Headache	21/21(100%)	2/21(9.5%)	2/21(9.5%)	0/21(0%)	0/21(0%)
Body pains	19/21(90.5%)	1/21(4.8%)	1/21(4.8%)	0/21(0%)	0/21(0%)
Positive blood test results	14/21(66.7%)	3/21(14.3%)	1/21(4.8%)	0/21(0%)	0/21(0%)

The table 2, shows that in adults (male and female) headache was the predominant symptom (100%), followed by body pains (90.5%) and fever (85.7%). Pre-treatment blood test positivity rate was 66.7%. In Day 1 there was reduction of fever by over 66.7%, headache by 90.5% and body pains by 85.7% and blood test positivity by 52.4 %. Full parasite clearance was achieved in Day 3 of follow up or after 4 days of treatment, with corresponding clearance of symptoms. By day 4 of follow up all symptoms were cleared. No statistical significance was observed in the results observed .

Table 3: Bio-Normalizer Treatment Outcome of Child Uncomplicated Malaria Patients in the National Capital District , Papua New Guinea, 2002-2003.

	Days of Follow Up and Treatment				
	0	1	2	3	4
Symptoms Present					
Fever	5/5(100%)	2/5(40%)	1/5(20.%)	1/5(20%)	0/5(1.%)
Headache	5/5(100%)	2/5(40%)	2(5%)	0/5(0%)	0/5(0%)
Body pains	4/5(80%)	1/5(20%)	0/5(1%)	0/5(0%)	0/5(0%)

Positive blood test	2/5(40%)	1/5(20%)	0/5(0%)	0/5(0%)	0/5(0%)

The table 3, shows that in children (male and female) fever and headache were the predominant symptoms with 100% of study participants presenting with it , followed by body pains (79%). Pre-treatment blood test positivity rate was 40% . In Day 1 of follow up , there was reduction of fever by over 60%, headache by 60% and body pains by 70% and blood test positivity by 20 %. Full parasite clearance was achieved in Day 2 of follow up or after 3 days of treatment, with corresponding clearance of headache and body pains. At full clearance of parasitaemia, fever still persisted in 20% of the study participants. By day 4 of follow up fever was cleared . Again no statistical significance was observed in these results.

Table 4: Bio-Normalizer Treatment Outcome of Female Uncomplicated Malaria Patients in the National Capital District , Papua New Guinea, 2002-2003.

	Days of Follow Up and Treatment				
	0	1	2	3	4
Symptoms Present					
Fever	6/8(75%)	1/8(12.5%)	0/8(0.%)	0/8(0.%)	0/8(0.%)
Headache	8/8(100%)	1/812.5%)	0/8(5%)	0/8(0%)	0/8(0%)
Body pains	6/8(75%)	1/8(12.5%)	0/8(1%)	0/8(1%)	0/8(0%)
Positive blood test results	4/8(50%)	1/8(12.5%)	0/8(0%)	0/8(0%)	0/8(0%)

The table 4, shows that in female patients (child and adult) headache was the predominant symptoms of with 100% of the study participants with it, followed by fever and body pains with 75% each. Pre-treatment blood test positivity rate was 50%. In Day 1 of follow up there was reduction of fever by over 52%, headache by 87.5% and body pains by over 52% and blood test positivity by over 37%. Full parasite clearance was achieved in Day 2 of follow up or after 3 days of treatment, with corresponding clearance of all symptoms. Again no statistical significance was

observed in these results.

Table 5: Bio-Normalizer Treatment Outcome of Male Uncomplicated Malaria Patients in the National Capital District , Papua New Guinea, 2002-2003.

	Days of Follow Up and Treatment				
	0	1	2	3	4
Symptoms Present					
Fever	17/18(94.4%)	5/18(27.8%)	1/18(5.6%)	1/18(5.6%)	1/8(5.6%)
Headache	18/18(100%)	3/18(16.7%)	2/18(11%)	0/18(0%)	0/18(0%)
Body pains	17/18(94.4%)	1/18(5.6%)	1/18(5.6%	0/18(0%)	0/18(0%)
Positive blood test results	12/18(66.7%)	4/18(22.2%)	2/18(11.1%)	0/18(0%)	0/18(0%)

The table 5, shows that in male patients (child and adult) headache was the predominant symptoms with 100% of the study participants presenting with it, followed by fever and body pains with 94.4% each. Pre-treatment blood test positivity rate was 66.7%. In Day 1 of follow up fever was reduced by 56%, headache by 83% and body pains by 88% and blood test positivity by 44 %. Full parasite clearance was achieved in Day 3 of follow up or after 4 days of treatment and maintained to the end of follow up, with corresponding clearance of head ache and body pains. Fever persisted in over 5% of the study subjects. Again no statistical significance was observed in these results.

Table 6: Bio-Normalizer Treatment Outcome of Uncomplicated Plasmodium falciparum Malaria in Adult Patients in the National Capital District , Papua New Guinea, 2002-2003.

	Days of Follow Up and Treatment				
	0	1	2	3	4
Symptoms Present					
Fever	8/10 (80%)	4/10(40%)	1/10(10%)	1/0(10%)	1/10(10%)
Headache	10/10(100%)	3/10(30%)	1/10(10%)	0/10(0%)	0/10(0%)
Body pains	9/10(90%)	1/10(10%)	0/10(0%)	0/10(0%)	0/10(0%)
Positive blood test Results	10/10(100%)	3/10(30%)	0/10(10%)	0/10(0%)	0/10(0%)

The table 6, shows that headache is the most prominent symptom of study participants with P.falciparum with all ten or 100% of the study subjects presenting with it, followed by body pains with 90% and fever in 8 or 80% of the study participants. All 10 (100%) of study participants were had pre-treatment blood test positivity with P.falciparum malaria. In Day 1 of follow up fever was reduced by 50%, headache by 70% and body pains by 80% and blood test positivity rate by 70 %. Full parasite clearance was achieved in Day 2 of follow up or after 3 days of treatment and maintained to the end of follow up, with corresponding clearance of body pains. Fever persisted in 10% of the study subjects even at the first day of full parasite clearance and lasted until the end of follow up. Head ache persisted in 10% of the study participants on the first day of full parasite clearance but disappeared from Day 3 of follow up and this was sustained till the end of the follow up period. Again no statistical significance was observed in these results.

A similar analysis as seen in table 6 was carried for in children and adult study participants . Of the 10 cases of P.Falciparum malaria, 9 were adult study participants and 1 was a child study participant All the children full parasite and all symptoms clearance were achieved in Day 2 of

follow up or after three (3) days of treatment with BN and these observations were sustained to the end of the follow up period. For the 9 adults study participants with P.falciparum malaria, full parasite and body pain clearance was achieved in on the same day as observed in children and fever and headache persisting in 1 out of 9 or 11% of the study participants at the day of full parasite clearance and cleared the second day after parasite clearance and this effect was sustained to the end of the follow up period.

Discussions:

This study had three major findings. First, there is a marked reduction of parasitaemia and symptoms of malaria after the first day of treatment with Bio-Normalizer for the general study population and this is further observed when analysis was stratified for age (child, adults) and gender and malaria parasite type. The symptom of body pain appeared to be the most responsive to the BN with the greatest reduction and faster clearance followed by headache and fever. Fever persisted in one (1) or 3% of the study population even after adequate clinical response and cure and it lasted through out the follow up. This may have been due to other febrile conditions not excluded during pre- treatment clinical examination and or due to reporting bias or both. Second Adequate Clinical Response to the agent was achieved in 23 out of 29(79.3%). This outcome was maintained when the data was stratified for age, gender and parasite type. Clinical cure of malaria occurred after 4 days of treatment in the general study population, but when stratified, clinical cure in children and female study participants occurred earlier ie after 3 days of treatment and for male study participants after 4 days of treatment. Taking only study participants with P.falciparum malaria, clinical cure was observed earlier, ie only after three (3) days of treatment Third there were no evidence of early treatment failure .Forth there were no evidence of side effects with the use of this agent in any of the study subjects.

The findings of this study generally agree with of that conducted by Jayatilaka et al in 1998-99,Therepeutic Efficacy of Chloroquine or Amodiaquine in Combination with Sulfadoxine – Pyrimethamine for Uncomplicated Falciparum Malaria in Papua New Guinea. This study showed a drop in fever/symptoms by 99.2% on Day 2 of treatment and 100% from day 3 onwards. In our study fever alone dropped by 79% in Day 2 and almost 100% in day 3 onwards. If fever plus other symptoms were analyzed in our study, as in the Jayatilaka et al study, the clearance would be better than that observed in that study. ACR obtained in the Jayatilaka et al study was 399/418 (95.4%) and in our study it was 23/29 (79.3%). The Jayatilaka et al study applied the full follow up period of 14 days where as our study only followed the patients for 4 days after initial treatment. The difference as observed in ACR was due to duration of follow up and number of end points met. If follow up had been longer even better results than that of Jayatilaka et al would have been observed. The Jayatilaka study did not did not look at prevalence of side effects ,ours did and we did not document any side effects.

Strengths and Weaknesses of the Study:

Weakness:

The sample size in our study is small and consequently the findings were not significant and this does not mean that the agent (BN) is not effective against the parasite, we believe it is and a larger sample size will demonstrate this. Next the follow up period in the study was only 4 days and not 14 days as recommended limiting the full application of the definition of ACR , ETF and LTF. We intentionally chose 4 days follow up period, as the aim of the study was to take a quick and crude assessment of the efficacy and safety of the agent to form the basis for future studies and also to monitor closely the efficacy in first five days of infection which we consider are important in so far as patient and therapeutic response is concerned as this we believe determines the agent usefulness, acceptability and usage and end stage outcome on the malaria parasite . Further to ensure patient compliance which we believe can be achieved reliably with shorter follow up periods

than longer ones. The other limitation was that our study was based more clinical symptoms related by the study participants and therefore the data is subjected to recall bias which could have influenced our results.

The strength of this study is that we were able to maintain daily monitoring of the effect of the agent for the first five days of infection which we consider are crucial (for reasons mentioned above) on the malaria parasite through daily blood slide microscopy and consequently we were able to closely document dramatic drops and clearance in parasitaemia and malaria symptom types. We were able also to document the absence of any side effects in this period which is crucial to patient compliance to treatment with this agent.

The other strength of the study is the follow period is short and patient compliance to the agent (BN) have been fairly good and consequently the treatment outcomes detected we believe are true outcomes. The possible effect of confounding by gender, age and parasite type on the treatment outcome were accommodated through stratified analysis and the treatment outcomes irrespective of the effect of these variables have been similar through out each stratum.

Conclusions and Recommendations:

We conclude that Bio-Normalizer is efficacious and safe in the treatment of uncomplicated malaria caused by Plasmodium falciparum and other malaria parasites in Papua New Guinea. The use of this agent is expected to increase patient compliance as there is no side effects related to its use and this is further enhanced as this agent can bring rapid symptom relief with corresponding action on the malaria parasite within 24 hours of treatment. The use of this agent for first line treatment is expected to reduce the number of treatment failures, the incidence of severe malaria and malaria mortality in Papua New Guinea.

We recommend further studies with 14-28 day follow ups to monitor resistance and recrudescent

patterns with its use and studies to document its long term effects on immunity status of persons *treated with this agent.*

Acknowledgement:

The study was funded by Bio-Normalizer PNG Ltd. The authors are very grateful to the clinical and technical staff of the National Department of Health who assisted in the study in the National Capital District. The support and assistance by the OIC of Haematology Laboratory of the Port Moresby General Hospital to conduct microscopy examination of all the blood slides is greatly acknowledged. The encouragement and support of Dr Nicholas Mann Secretary for Health is also greatly acknowledged. The Advise from Professor James Osato, the founder of Bio-Normalizer is very much appreciated.

References

1. Papua New National Health Plan 2000-2010
2. K.D.P Jayatillaka et al ; Therapeutic Efficacy of Chloroquine or Amodiaquine in
3. Combination with Sulfadoxine –Pyrimethamine for Uncomplicated Falciprum Malaria in Papua New Guinea, 1998-1999.
4. BRUE-CHWATT et al. WHO Monograph series No. 27.
5. Z. Premji, Clinical Trial to Determine the Efficacy of Anti-Malarial Drugs by Clinical and Parasitological Indicators, in Tanzania, A Generic Protocol.