Published by: IPS Intelligentsia Publishing Services ***Available online:*** *https://tjansonline.com*

Tropical Journal of Applied Natural Sciences
Trop. J. Appl. Nat. Sci., 3(2): 14-18 (2021)
ISSN: 2449-2043
https://doi.org/10.25240/tjans.v3i2.3
Published as part of the 1st Faculty of Basic Medical Sciences (FBMS) Scientific Conference Papers

Comparative Assessment of Adverse Effects of Synergistic Combination of Pyrimethamine and Sulfadoxine (Fansidar/Maloxine) in Patients Studied in Abakaliki, Ebonyi State, Nigeria

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ABSTRACT

Adverse effects of antimalarial drugs, which were commonly attributed to chloroquine such as: headache, various skin eruptions, Pruritus, Gastro-intestinal disturbances such as nausea, and vomiting. Others, such as: mental changes involving psychotic episodes, anxiety, visual disturbances such as blurred vision, keratopathy or retinopathy. Some common side effects like loss of hair, ototoxicity, photosensitivity, tinnitus, neuro-myopathy, myopathy, erythema multiformes and Stevens-Johnson syndrome, hemolysis and blood dyscrasias, Neutropenia etc., are still reported in some patients treated with the Pyrimethamine and Sulphadoxine drug combination. The emergence of combination therapeutic approach to malaria treatment was believed to have reduced the frequency of these events, but most, still persist. This survey was conducted to therefore, assess the overall presentation of Diarrhoea, Pruritus and Vomit in Patients treated with Maloxine and Fansidar. At Day zero, (D0), 40(15.0%) Presented positive Diarrhoea cases; 05(1.9%) present positive cases of pruritus and 73(27.4%) presented positive cases of vomit. At Day 2, (D2), 03(1.1%) presented positive Diarrhoea cases as against 263(98.9%) of negative cases; 01(0.4%) presented positive cases of pruritus as against 265(99.6%) of negative cases. Day Seven, (D7) and Day Fourteen, (D14) recorded clearance of the adverse effects. There is therefore need for relevant drug treatment follow up to clear the adverse effects engendered by malaria drug therapy.

Original Research Article

Received: *14th Jun, 2021*
Accepted: *24th Jul, 2021*
Published: *30th Sept, 2021*

Keywords:
Synergistic
Pyrimethamine
Sulphadoxine
Diarrhoea
Pruritus

1. INTRODUCTION

Malaria is a parasitic infection of red blood cells and the liver caused by four related species: *Plasmodium (P.) falciparum, P. vivax, P. oval and P. malariae* (WHO, 1990). Malaria has considerable potential for adversely influencing nutrition vis-à-vis; it can restrict food intake through anorexia, while causing gastrointestinal problems associated with vomiting or diarrhea (Franklin *et al*., 1984). It has been reported by WHO (1997), that administration of diaminopyrimidines and sulphonamide drugs against malaria parasites induce

gastrointestinal problems occasioned by Diarrhoea, central nervous system stimulation with vomiting, excitability, itching particularly aquagenic pruritus, dizziness, insomnia ,convulsion etc.

In the opinions of Gellert *et al.* (1998) and Aguwa (1996), the administration of antimalarials can cause vomiting disturbances due to gastrointestinal discomfort caused by the drug. The issue of Steven Johnsons syndrome which affects the scrotal sac of males is an indication of the hypersensitivity of the drugs interactions in the human body, particularly the sulphonamides as contraindicated by the drug manufacturers themselves i.e Roche Pharmaceuticals. Numerous other adverse effects of antimalarial drugs include various skin eruptions, mental changes including psychotic episodes, anxiety, visual disturbances such as blurred vision, keratopathy, (common with chloroquine drug), the uncommon side effects include loss of hair, photosensitivity, tinnitus, neuromyopathy and myopathy, eryrthema muitiforme and Stephen Johnsons syndrome, others include haemolysis and blood dyscrasias, Neutropenia. More so, Rapid intravenous administration can result in cardiovascular toxicity and death may occur (Martindale, 1996).

2. MATERIALS AND METHODS

2.1 The two choice of drugs formulation for the study:

Fansidar and Maloxine were administered orally, three tablets as a dose treatment as recommended by the manufacturers. The drugs were only given when the patient tested positive to malaria infections, while malaria negative persons were excluded from the study.

To successfully evaluate adverse drugs effects associated with drug therapy the following conditions were assessed on each encounter with the patients:

2.2 Vomit: patients were observed at least 30 minutes after each treatment. At each subsequent visit, the patient was asked whether he/she has vomited since the the last visit? If the drugs was vomited or spit out, the estimated lost portion of dose was readministered. When vomiting tendency continued in some patients, they were excluded from the study.

2.3 **Pruritus**: pruritus for the purpose of the study was itching which occurs after the administration of the anti-malarial drugs under study and which was not attributed to another medical condition or other drug therapy. Patients with pruritus conditions were evaluated and decisions made on whether to continue with drugs under study and possible anti-histamine to apply. Anti-histamine drugs of choice for the study were Piriton and Phenergen (promethazine) other such as Mepyramine (Pyrilamine), chlorcylizine (histantin), Diphenyl-hydramine (Benadryl) and chlorpheniramin (chlortrimetin) were slated for use if the need arose, but were not seen over the counter in the study area.

2.4 Diarrhoea: Diarrhoea for the purpose of the Study was defined as passage of more than three unformed stools in 24 hours period. The patients were asked at each day of activity about the occurrence of this condition during the previous 48 hours.

2.5 Activity and follow up Analysis

The Assessment protocol of the research was based on the 14 day Clinical and Parasititological responses to supervised therapies as was developed by WHO (5,6) in 1990 modified by CDC (7,8) in 1991.

Standard therapy consisted of potency tested fansidar and maloxine base per Kg of body weight administered orally on “Day O” (DO). Blood Flims Temperature, weight and overall clinical evaluations were conducted as shown below:

Activity	DAYS						
	0	1	2	3	7	14	RMK
Blood film taken	X	-	X	*	X		X
Temperature taken	X	X	X	*	X		X
Weight recorded	X	X	X	*	X		X
Drugs given	X	-	-	-	-		-
Diarrhoea checked	X	X	X	*	X		X
Vomiting checked	X	X	-	-	-		-
Assessment of patients health	X	X	X	*	x		X

https://doi.org/10.25240/tjans.v3i2.3

Source:WHO(1990). Legend: (x)= Perform Activity (-)=No Activity

(*)=Optional

3. RESULTS AND DISCUSSION

Table 1: Shows overall presentation of Diarrhoea, Pruritus and Vomit in fansidar patients. At D0, 99 (38.9%) presented Diarrhoea cases. 43 (16.7%) presented positive cases of pruritus and 29 (11.2%) presented positive cases of vomit. At D2, 37 (14.3%) presented positive Diarrhoea cases as against 221 (85.7%) of negative cases; 50 (19.4%) presented positive cases as against 208 (80.6%) of negative cases.

Table 1: Overall presentation of Diarrhoea/Pruritus and vomit in fansidar patients

	Diarrhoea				Pruritus				Vomit			
	+ve	%	-ve	%	+ve	%	-ve	%	+ve	%	-ve	%
D0	99	38.9%	159	61.6%	43	16.7%	215	83.3%	29	11.2%	229	88.8%
D2	37	14.3%	221	85.7%	50	19.4%	208	80.6%	0	0	0	0
D7	0	0	0	0	0	0	0	0	0	0	0	0
D14	0	0	0	0	0	0	0	0	0	0	0	0

Table 2 shows overall presentation of Diarrhoea, Pruritus and Vomit in maloxine patients. At 40 (15.0%) presented positive Diarrhoea cases 05 (1.9%) presented positive cases of pruritus and 73 (27.4%) presented positive cases of vomit. At D2, 03 (1.1%) presented positive diarrhoea cases as against 263 (98.9) of negative cases, 01 (0.4%) presented positive cases of pruritus as against 265 (99.6%) of negative cases.

Table 2: Over all presentation of Diarrhoea/Pruritus and vomit in Maloxine Patients.

	Diarrhoea				Pruritus				Vomit			
	+ve	%	-ve	%	+ve	%	-ve	%	+ve	%	-ve	%
D0	40	15.0%	266	85.0%	05	1.9%	261	98.1%	73	27.4%	193	71.6%
D2	03	1.1%	263	98.9%	01	0.4%	265	99.6%	35	13.2%	231	86.8%
D7	-	-	266	100%	-	-	-	-	-	-	-	-
D14	-	-	266	100%	-	-	-	-	-	-	-	-

Table 3 shows positive and negative Diarrhoea record for both male and female maloxine Patients. Out of 156 (58.6%) of males sampled 24 (15.4%) as against 132 (84.6%) has positive cases at D0 and 03 (1.9%) against 153 (98.1%) on D2. Out of a total 110 (41.4%) females, 16 (14.5%) against 94 (85.5%) had positive cases at D0 and 0.0 (0.0%) against 110 (100 %) cases at D2.

Table 3: Diarrhoea presentation in Male/Female Maloxine Patients

Sex	Pop.	%	D0				D2				D7				D14			
			+ve	%	-ve	%	+ve	%	-ve	%	+ve	%	-ve	%	+ve	%	-ve	%
Male	156	58.6%	24	15.4	132	84.6	03	1.9	153	98.1	-		156	100	-	-	156	100
Female	110	41.4%	16	14.5	94	85.5	-	-	110	100	-		110	100	-	-	110	100
Total	266	100%	40	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 4 shows positive and negative cases of Pruritus for male and female maloxine patients. Out of 156 (58.6%) of males sampled 03 (1.9%) against 153 (98.1%) had positive cases at D0 and 0.0 (0.0%) against 0.0 (0.0%) on D2, out of a total of 110 (41.4%) females, 01 (0.9%) against 0.0 (0.0%) had positive cases at D0 and 0.0 (0.0%) against 0.0 (0.0%) positive cases at D2.

Table 4: Check for Pruritus in Maloxine Patients

Sex	Pop.	%	D0	D2	D7	D14

			+ve	%	-ve	%	+ve	%	- ve	%	+ve	%	- ve	%	+ve	%	- ve	%
Male	156	58.6%	03	1.9	153	98.1	-	-	-	-	-	-	-	-	-	-	-	-
Female	110	41.4%	01	0.9	109	99.1	-	-	-	-	-	-	-	-	-	-	-	-
Total	266	100%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 5 shows comparative Assessment of Diarrhoea on fansidar and maloxine patients. In males, fansidar patients had 57.0% of Diarrhoea cases against 17.3% of maloxine patients. In females, fansidar patients had 46.7% against 14.6% of maloxine patients.

Table 5: Comparative Assessment of Diarrhoea on Fansidar and Maloxine Patients.

Drugs	Male	%	Female	%
Fansidar	86	57.0%	50	46.7%
Maloxine	27	17.3%	16	14.6%

Table 6 shows comparative Assessment of pruritus in fansidar and maloxine patients. In males, fansidar patients had cases of 37.1% against 1.9% of maloxine patients. In the female category, fansidar patients had 33.6% against 0.9% of maloxine Patients.

Table 6: Comparative Assessment of Pruritus in Fansidar and Maloxine Patients.

Drugs	Male	%	Female	%
Fansidar	56	37.1%	36	33.6%
Maloxine	03	1.9%	01	0.9%

Table 7 shows comparative Assessment of vomit in fansidar and maloxine patients. In the males, fansidar patients had 11.9% of positive cases against 45.5% of maloxine patients. In the female category, the fansidar patients had positive cases of 9.4% against 30.0% of maloxine patients.

Table 7: Comparative Assessment of vomit in Fansidar and Maloxine Patients.

Drugs	Male	%	Female	%
Fansidar	18	11.9%	10	9.4%
Maloxine	71	45.5%	33	30%

In line with the findings of this assessment study, diaminopyrimidine and sulphonamides are considered efficacious against malaria parasites but also present unpleasant side effects. In the follow up analysis of the investigation, diarrhea, pruritus and vomiting variance in patients treated with either of the drugs show similar trends. The gastrointestinal problems occasioned by diarrhea was presented in the patients (Tables 1-7) this no doubt related to the findings of Martindale (1996), WHO (1997), that administration of pyrimethamine formulation as antimalaria therapeutic measure may induce gastrointestinal effects and central nervous system stimulation with vomiting, excitability and convulsions.

The opinions of Gellert *et al.* (1998) and Aguwa (1996) were confirmed in the investigation that nearly 10.8% of the patients treated with fansidar suffered vomiting disturbances at Day Zero (DO) of drug administration occasioned by gastrointestinal disturbances (Table 1, 7).

In maloxine therapy, only 2.8% of the patients suffered abdominal discomforts occasioned by vomits. This further supported the findings of Molyneaux (1997) that suphonamide/pyrimethamine drug combination induces gastrointestinal discomfort that can induce vomits in patients treated with such drug formulation. Pruritus, particularly, aguagenic puritus was recorded after fansidar treatment at Day Zero (DO) (16.3%) and Day two (D2) (19.4%) which cleared at D7 and D14 (Table 6) whereas in Maloxine treated patients, pruritus was recorded for DO (2.8%) which cleared as from D2, appear to align with the claims of Tray and Webster (1996) that prolonged usage of pyrimethamine in drug combination can induce rashes and hypersensitive reactions.

CONCLUSION

In this study, several adverse effects of antimalarial drug administrations was observed which includes cases of diarrhea, pruritus, vomiting and so on. As an illustration, it was found that at day zero (D0), 40(15.0%) presented positive diarrhoea cases, 05(1.9%) presents positive cases of pruritus and 73(27.4%) presented positive cases of vomit. At Day 2 (D2), 03(1.1%) presented positive Diarrhoea cases as against 263(98.9%) of negative cases; 01(0.4%) presented positive cases of pruritus as against 265(99.6%) of negative cases. While at day seven (D7) and day fourteen (D14) there was clearance of the adverse effects.

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How to cite this article

Ikeh, I.M., Odikamnoro, O.O., Okonkwo, V.O. and Nnatuanya I.O. (2021). Comparative Assessment of Adverse Effects of Synergistic Combination of Pyrimethamine and Sulfadoxine (Fansidar/Maloxine) in Patients Studied in Abakaliki, Ebonyi State, Nigeria. *Tropical Journal of Applied Natural Sciences*, 3(2): 14-18. https://doi.org/10.25240/tjans.v3i2.3