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RESEARCH PAPER

EFFECTS OF SEPTRIN ADMINISTRATION ON BLOOD CELLS PARAMETERS IN HUMANS

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ABSTRACT

The hematological changes associated with septrin administration in humans were investigated. One hundred (100) male patients (aged 18-40 years) who were placed on the therapeutic dose of septrin were divided into four groups based on the prescribed duration of their septrin intake. Twenty (20) healthy males served as the control. At the end of the treatment period, blood was obtained from each subject for the estimation of blood parameters following standard procedures. The results showed that the packed cell volume (PCV), total white blood cell count (WBC), neutrophils and platelets were significantly decreased ($p<0.05$), especially after 7-10 days of septrin administration, compared to the control values. On the other hand, the reticulocytes, lymphocytes, eosinophils and prothrombin time (PT) showed significant increases ($p<0.05$), compared to the value for the control. The observed changes in blood parameters in this study were all duration-dependent. It is concluded that septrin administration can cause alterations in blood parameters, and these duration-dependent changes should be put into consideration when recommending its intake.

Key words: ***Septrin, Hematological parameters, Humans. Therapeutic dose***

INTRODUCTION

Septrin is a brand name for a combination of antibiotics called cotrimoxazole. The drug is composed of two active principles: trimethaprim and sulphamethoxadole, and used to prevent/treat pneumocystis carinii pneumonia, PCP (Jaffe *et al*., 1983).

Sulphamethoxadole is a structural analogue of p-amino benzoic acid (PABA), which is essential and required for the synthesis of folic acid- precursors of deoxyribonucleic acid (DNA) and RNA in both bacteria and mammals, with the later obtaining their folate from the diet and not from PABA. Sulphamethoxadole works by competing with PABA for the enzyme dihydropteroate synthetase (Howland and Mycek, 2007). In this way, it inhibits the growth of bacteria (i.e. it is bacteriostatic).

On the other hand, 'Trimethoprim' interferes with the ability of bacteria to metabolize folinic acid, thus exerting a bacteriostatic activity. Trimethoprim is a folate antagonist, which inhibits the conversion of dihydrofolate to the desired form (tetrahydrofolate) by the key enzyme dihydrofolate reductase, which is extremely sensitive to trimethaprim (Roach and Scherer, 2000).

Sulphamethoxadole and trimethaprim therefore, affects two stages in the same metabolic pathway for folate synthesis in bacteria (in the form of a double barrel attack). Septrin is a widely used effective antibacterial drug by adults and children. The indications for septrin usage include urinary tract infections (Stamm and Hoosten, 1993),

typhoid, bacterial diarrhea (Wormser *et al*., 1982), dysentery and PCP (Tripathi *et al*., 2001). However, in spite of its efficacy, septrin administration has been associated with side effects that include anemia and other changes in some hematological parameters. Reported side effects of sulphamethoxadole include hemopoietic disturbance (bone marrow depression), hemolytic anemia in patients with glucose phosphate dehydrogenase deficiency (Champe *et al.,* 2000), granulocytopenia and thrombocytopenia (Howland and Mycek, 2007). On its part, trimethaprim administration can produce the effects of folic acid deficiency, marked by megaloblastic anemia, leukemia and granulocytopenia, especially in pregnant patients and those on poor diet (Rang *et al*, 2000). This study was therefore, embarked upon to investigate the pathophysiology of some of the treatment-induced changes in blood parameters following septrin administration.

MATERIAL AND METHODS

Study population: This study was carried out at the Irrua Specialist Hospital Irrua, Edo State, Nigeria (a tertiary health institution used as a Teaching Hospital for the College of Medicine of Ambrose Alli University, Ekpoma, Edo State). Out and in-patients who attended the hospital during the periods of study were randomly selected for this investigation. The control group was randomly selected from staff of the hospital.

Ethical consideration: A written approval by the Ethics Committee of the Teaching Hospital was sought and obtained for this study. Secondly, an informed consent by all the subjects was obtained before the start of the study.

Study design: A total of 120 males, aged between 18 and 40 years, were used for this study. The test group consisted of one hundred (100) male out-patients and in-patients, who were placed on the therapeutic doses of septrin. The control was made up of 20 apparently healthy males, aged between 18 and 40 years, who were not on any medications during the period of the study. The test group was divided into four categories of 25 persons each, according to the duration of septrin administration. The categories were: 3-6 days, 7-10 days, 11-13 days, and above 14 days.

Collection of Blood Sample: Venous blood was obtained from each subject and dispensed into specimen bottles that contained 0.2mls of 10% EDTA. The contents were well mixed immediately, labeled and used to carry out the following investigations: packed cell volume (PCV), total white blood cell (WBC) count, platelet count, reticulocyte count, differential WBC count, and prothrombin time (using plasma from the blood sample, immediately, to determine the time it took for clot to form).

Sample Analyses: The packed cell volume (PCV), white blood cells count (WBC), differential WBC count and Platelet count (PC) were estimated by the method of Dacie and Lewis (1990). For the prothrombin time, an aliquot (0.1ml) of the blood sample from each subject was dropped individually into test tubes numbered 1-10. Thereafter, 0.1ml of commercially prepared control sample was dropped into tube number 11. All the tubes were warmed at 37^{o}C for 3mins (tube 11 for 5mins). Subsequently, 0.2ml of prothrombin reagent was added to each test tube; and the clotting time was observed and recorded for each tube. Standard laboratory procedures were followed for all the experiments in the study.

Statistical Analysis: The result of the experiment was statistically analyzed using SPSS windows version 16 software. The results are presented as means ± SEM. Student's t-test was used to test for significance. P values of <0.05 were considered as significant.

RESULTS

The results of the investigation show that septrin administration caused increases in some and decreases in other hematological parameters. Specifically, PCV was significantly ($p<0.05$) decreased, especially, in the subjects that were on septrin administration for 10-13days and above. The mean PCV values range from 40.00±3.32% in 3-6 days of treatment to 35.0±4.10% in above 14 days, compared with the control value of 40.0±3.32%. The mean total white blood cell count was significantly reduced, in a duration-dependent manner, from 5.50±1.71UI in 3-6 days of septrin administration to 3.90±0.45UI in above 14 days of intake, when compared with the mean control value of 6.0±1.51UI.

The mean platelet count also significantly reduced, as treatment duration increased, from 176.80±19.39UI after 3-6 days to 97.20±13.60 after 14 days, compared with the mean control value of 201.90±26.30. The neutrophils number

decreased, as duration of administration increased, from mean value of 61.0±7.64UI after 3-6 days, to 40.0±8.36UI after 14 days; while the mean control value was 62.0±8.40UI. This represents a maximum percentage decrease of 35.5% in more than 14 days of treatment, compared to the mean control value.

The hematological parameters that were significantly increased due to septrin administration include the following: reticulocyte count, lymphocytes, eosinophils, and prothrombin time. The mean reticulocyte count increased significantly ($p<0.05$), from 0.80±0.33 (or 25.0%) after 3-6 days of treatment to 1.0±0.56 (or 40.0%) after more than 14 days of treatment, compared to the mean control value of 0.60±0.17. The increase in the lymphocytes in blood ranged from 39.0±7.32 after 3-6 days of septrin administration to 57.20±8.26 after more than 14 days of treatment, compared to the mean control lymphocyte value of 38.0±0.37. This shows significant increases of 25.5% and 38.6%, after 11-13 days and above 14 days of septrin administration, respectively. The eosinophil in the treated subjects increased significantly by 42.3% (0.26±0.45) after 3-6 days and by 88.4% (1.3±2.23) after 14 days of treatment, compared to the mean control eosinophil value of 0.15±0.37.

The results of the basophils (0.10±0.31) and monocytes (0.10±0.31) in the blood of the treated subjects did not change during the treatment period, when compared to the respective mean control values. The result of the prothrombin time showed significant increases which ranged from12.60±1.96 after 3-6 days of treatment, to 16.80±1.40 after over 14 days of treatment, compared to the mean control value of 11.35±1.31. This represent a range of 12.70% - 30 40% increase in prothrombin time, compared to the control value.

Table 1. Mean values and percentage changes in blood parameters in human subjects during Septrin administration

		Durations of Septrin Administration			
Index	**Control**	**3 – 6 Days**	**7 – 10 Days**	**11 – 13 Days**	**Above 14 Days**
PCV	42.0±3.14	40.0±3.32	40.0±2.32	37.0±3.68*	35.0±4.10*
(% change)		**(-4.76)**	**(-4.76)**	**(-11.90)**	**(-16.70)**
WBC	6.0±1.51	5.5±1.71	5.8±0.84	4.10±0.18*	3.90±0.45*
(% change)		**(-8.30)**	**(-3.30)**	**(-31.70)**	**(-35.00)**
Platelet	201.9±46.30	176.8±19.39	167.6±27.17	108.0±8.37*	97.2±13.60*
(% change)		**(-12.43)**	**(-16.99)**	**(-46.50)**	**(-51.90)**
Reticulocyte	0.60±0.17	0.80±0.32	0.70±.24	0.90±0.38*	1.0±0.56*
(% change)		**(+25.00)**	**(+14.30)**	**(+33.30)**	**(+40.00)**
Neutrophil	62.0±8.40	61.0±7.64	60.0±7.90	47.0±6.65*	40.0±8.36*
(% change)		**(-1.61)**	**(-3.23)**	**(-24.20)**	**(-35.50)**
Lymphocyte	38.0±0.41	39.0±7.32	39.0±7.32	51.0±8.76*	57.2±8.26*
(% change)		**(+2.60)**	**(+2.60)**	**(+25.50)**	**(+38.60)**
Eosinophil	0.15±0.37	0.26±0.45*	0.26±0.45*	1.14±0.75*	1.30±2.23*
(% change)		**(+42.30)**	**(+42.30)**	**(+86.00)**	**(+88.40)**
Basophil	0.10±0.31	0.10±0.31	0.10±0.31	0.10±0.31	0.10±0.31
Monocyte	0.10±0.32	0.10±0.32	0.10±0.32	0.10±0.32	0.10±0.32
Prothr. Time	11.35±1.31	12.60±1.96	14.40±1.98*	16.80±1.31*	16.80±1.40*
(% change)		**(+12.70)**	**(+23.60)**	**(+30.40)**	**(+30.40)**

Data represented as Mean ±SEM ; *Significantly different from control, ($p<0.05$); - represent reduction/decrease; + represents addition/increase

DISCUSSION

The findings of this study demonstrated that septrin administration caused variations in some hematological parameters and the observed variations become more obvious with increase in the duration of treatment. The observed duration dependent decrease in the PCV of all the treatment groups is thought to be due to inhibition of folate metabolism by the drug. These results conform with previous reports by Christie (1999) that the adverse effects of septrin administration are related to the duration of treatment, and not always due to the administered dosage.

Interestingly, the total white blood cell (WBC) count decreased significantly, especially after 10 days of septrin administration at mean of $4.10\pm0.18x10^{-4}$, compared to the mean control value of $6.0\pm1.51x\ x10^{-4.}$ This duration-

dependent reduction in WBC count coincided with the observed pattern of decrease in the neutrophils in the present study. One can deduce that the observed reduction in neutrophils by 24.20% after 10 days of treatment, contributed to the observed 31.7% decrease in total white blood cell count at the same duration of septrin administration. This result supports the earlier report by Bloom and Small (1998) that prolonged septrin administration could lead to leucopenia in human subjects.

The significant duration-dependent decrease in platelet count may not be unconnected with the observed significant increase in the prothrombin time, since the prothrombin time is a function and product of the platelet number and aggregation activity (Fox, 1999). Schoring (1996) observed that septrin acts as haptens that bind platelets during their activity, but the decrease in platelet number in this study may have mitigated this property. The decrease in platelet number may also result from reduction in blood cell formation due to septrin-induced depression to bone marrow activity (Patrono, 1999). This effect on platelet may suggest that prolonged administration of septrin might indeed lead to development of thrombocytopenia – the effect of low platelet count. Septrin is believed to be an antagonist to folic acid metabolism, and this may predispose septrin users to folic acid deficiency, and thus, compromise the use of folic acid in WBC production, and may consequently lead to leucopenia (Bloom and Small, 1998).

Similarly, the significant duration-dependent decrease in neutrophil number may indeed be responsible for the observed decrease in total white blood cell count obtained in this study since it represent a major component of the WBC. On the contrary, reticulocyte number increased significantly in a duration-dependent manner after 11-13 days of treatment and this may represent hemopoietic response of the bone marrow to the observed reduction in packed cell volume reported earlier in the present study.

Furthermore, platelet count was significantly decreased in a duration-dependent manner; this outcome may be responsible for the observed significant increase in the prothrombin time recorded in this study. The 25.5% increased in lymphocyte number after 11-13 days may be a response to compensate for the decreases in neutrophils and white blood cells observed earlier in the present study, which may have given rise to the recruitment of lymphocytes which may cause acute lymphocytosis. The highest increase in blood cells in this study however, was observed in the eosinophils number which demonstrated significant rapid increase of 42.3% after just 3-6 days of administration, compared to the control value. This high increase in eosinophil count may have significantly contributed to the equally significant increase in the total WBC count.

Finally, prothrombin time (PT) was significantly increased in the subjects in a duration-dependent manner. The observed increase in PT may be related to the duration-dependent decrease in platelet count since the rate of blood coagulation is a function of platelet count and aggregation activity. It may also be a reflection of treatment-induced deficiency in either factors VII, X, V, or prothrombin (Ezeilo, 2009). Further studies are however, required to verify this possibility.

Conclusion

The therapeutic administration of septrin can cause a significant duration-dependent variation in blood cell parameters, and these unlisted side effects should be adequately put into consideration during its prescription. Further investigations are recommended so as to further evaluate the long term impact of these treatment-induced alterations in blood cell parameters.

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AUTHOR(S) CONTRIBUTION

Onyebuagu, P.C. was responsible for the design, data collection and editorship of this article. Kiridi, K. was in-charge of data analysis and interpretation, while Pughikumo, D.T. was involved in interpretation of data and discussion.