Volume 13 Issue 15
Originally issued as B4

Global Journal of Medical research
Pharma, Drug Discovery, Toxicology and Medicine
Volume 13 Issue 4 Version 1.0 Year 2013
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN : 0975-5888

Effect of Oral Administration of Chloramphenicol on Hematological Profile of Male Charles Foster Rats

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Abstract - For a given organism, relevant information about the internal environment can be easily accessed by its hematological profile. Chloramphenicol being a potent broad spectrum antibiotic is used readily in eyed drop formulations and is also in food industry. In the present study, varying doses (750, 1500 and 2250 mg/kg B.Wt) of Chloramphenicol (CAP) was administered orally as single daily dosage for 24 days to Male Charles Foster rats, to assess the hematological changes associated with oral exposure to the drug. The results showed a significant ($p<0.05$) dose dependent decrease in Red Blood Cells (RBC) count, Hemoglobin (Hgb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC) and increase in Hematocrit (Hct), White Blood Cells (WBC) and Platelets compared to the initial blood profile. The results recorded in this present study suggested that exposure to CAP results in Hematotoxicity. Hence, the potential of CAP to cause hematotoxicity is reported in the study.

Keywords : *CAP, hematotoxicity, blood cells, CF rats.*

GJMR-B Classification : *NLMC Code: WB 350*

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Effect of Oral Administration of Chloramphenicol on Hematological Profile of Male Charles Foster Rats

P. Shukla[α] & R. K. Singh[σ]

Abstract - For a given organism, relevant information about the internal environment can be easily accessed by its hematological profile. Chloramphenicol being a potent broad spectrum antibiotic is used readily in eyed drop formulations and is also in food industry. In the present study, varying doses (750, 1500 and 2250 mg/kg B.Wt) of Chloramphenicol (CAP) were administered orally as single daily dosage for 24 days to Male Charles Foster rats, to assess the hematological changes associated with oral exposure to the drug. The results showed a significant ($p<0.05$) dose dependent decrease in Red Blood Cells (RBC) count, Hemoglobin (Hgb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC) and increase in Hematocrit (Hct), White Blood Cells (WBC) and Platelets compared to the initial blood profile. The results recorded in this present study suggested that exposure to CAP results in Hematotoxicity. Hence, the potential of CAP to cause hematotoxicity is reported in the study.

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I. Introduction

Chloramphenicol (CAP) is a broad spectrum antibiotic, was first quarantined from bacterium *Streptomyces venezualae* in the year 1947. It was available by the trade name of Chloromycetin by Parke Davis & Co. It was prescribed in mass in 1948 in USA following an outburst of enteric fever. In 1949 it was cleared from Federal Food and Drug, since then it has been used and worked upon extensively being a potent inhibitor of protein synthesis (E. Cundliffe and K. McQuillen, 1967).

Some studies suggest the use of CAP in food. Although, most countries have banned CAP from animal food production, still traces of it have been detected in shrimp and other aquaculture products. According to regulations promulgated in 1980's and 1990's, use of CAP in food was banned and countries have established a zero tolerance policy. In Japan, zero tolerance thresholds for CAP is 50 ppb which in USA is 5 ppb. Meat and offal from treated animals contained CAP and its non – genotoxic metabolites (G. Milhaud, 1993).

Even being a potent antibiotic with a broad range of spectrum, the use of CAP is limited due to its association with aplastic anaemia (AA) (M. L. Rich, et al., 1950) and bone marrow suppression (C. E. Amberkar, et al., 2000). AA is a rare, dose independent, irreversible, idiosyncratic, manifestation of CAP which in most cases is seen years after the treatment (A. A. Younis, 1989 (a)) and is fatal (A. A. Turton, et al., 2002) risk of developing AA after CAP administration is 1:30000 to 1:5000015 (C. H. Li, et al., 2010). Only orally administered CAP leads to AA (R. Holt, 1967; R. A. Gleckman, 1975). This has made the CAP to be prescribed parenterally by many physicians. It is not known whether this lowers the incidence of AA or not but the risk is obviously lowered. Other than oral and parenterally absorbed CAP, it is also used as ophthalmic preparations where AA is also very rare (R. L. Rosenthal and A. Blackman, 1965; G. Carpenter, 1975; S. M. Abrams, et al., 1980)

Blood or hematological parameters are probably the more rapid and detectable variations under stress and are fuel in assessing different health conditions (V. Hymavathi and L. M. Rao, 2000). Hence, the significance of hematological parameters in clinical and experimental studies in life sciences cannot be overemphasized. Particularly, literature reports have proved that the alterations in the hematological parameters, from normal state/levels, may be used as valuable indicators of disease, or stress in different animal species (A. K. Solanke and V. Singh, 2000; B. K. Das and S. C. Mukherjee, 2003; L. H. Jee, et al., 2005; M. F. Rahman and M. K. Siddiqui, 2006; F. E. Uboh, et al., 2005).

Literature reports that hematological profile of different species of animals may be influenced adversely by phenylhydrazine (F. S. Sanni, et al., 2005; J. Berger 2005; S. K. Jain and D. Subrahmanyam, 1978), some antiretroviral drugs (A. A. A. Kayode, et al., 2011), Paclitaxel (J. A. Juaristi, et al., 2001), Carbamazepine (S. Thakur, et al., 2012), Doxorubicin (D. A. Eppstein, et al., 1989), Tetrachloroethylene (A. M. Emara et al., 2010), Phenacetin (C. B. Jensen and D. J. Jollow 1991) and Benzene (A. Beamonte et al., 2005; R. Synder and C. C. Hedli, 1996). Plants also have been shown to have ameliorative potential in reference to drug induced hematotoxicity (F. S. Sanni et al., 2005; E. E. Edet et al., 2011; E. V. Ikpeme et al., 2011; S. O. Kolawole et al., 2011, G. Prasad and G. L. Priyanka, 2011). Different

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extracts (methanolic, ethanolic, water, chloroform, hexane) of some plants namely, Hibiscus cannabinus (G. A. Agbor, et al., 2005), Brillantaisia nitens (P. A. Akah, et al., 2009(a), 2010(b)), Hibiscus sabdariffa (A. Ologundudu, et al., 2010), Zingiber officinale (A. M. M. Attia, et al., 2013), Ocimum basilicum (S. Saha. et al., 2012) and Ocimum gratissimum (A. W. Obianime, et al., 2011) have been reported to express a positive impact on the hematological profile of several animal species. Assessment of hematological parameters can therefore be useful in determining the extent of deleterious effects of foreign substances on the blood parameters of an animal. The present investigation was therefore aimed at assessing the effect of Chloramphenicol on the hematological profile in Charles Foster male rats.

II. Materials and Methods

a) Administration of Material

The chloramphenicol Capsules IP manufactured by Piramal Health Care Limited (Batch No-9BE012) were used for the study. Freshly prepared chloramphenicol suspension was administered orally by cannula for 24 days.

b) Animals

Albino rats of *Charles Foster* strain were used in the study. IAEC approval number was taken from the Institutional Animal House Facility which is affiliated to and works under the guidelines of CPCSEA (No. 36/11/Toxicol/IAEC). Rats weighed between 120- 150 grams and were housed in polypropylene, autoclavable cages (dimensions: 43x27x15 cm) with steel wire-mesh lid having provisions for attaching water bottle and for keeping food pellets. Animals had continuous access to food and water during the entire period of experimentation. They were examined routinely for their body weights and hematological parameters.

c) Experimental Design

20 rats showing evidences of good health were selected on the basis of findings of their initial health check-up and body weight recordings. They were randomly assigned to four treatment groups, each group consisting of five male animals and one group comprising of an equal number of animals served as control.

Group I: Control (Distilled water)
Group II: Low Dose (750 mg/ kg B.wt CAP)
Group III: Mid Dose (1500 mg/ kg B.wt CAP)
Group IV: High Dose (2250 mg/ kg B.wt CAP)

d) Hematological Investigations

Blood collected from the caudal vein of experimental animals was assessed for all hematological parameters RBC (Red Blood Cell), Hgb (Hemoglobin), MCV (Mean Corpuscular Volume), MCHC (Mean Corpuscular Hemoglobin Concentration), Hematocrit (Hct), White Blood Cells (WBC) and Platelets. Blood analysis was performed at regular time intervals using fully automatic hematology analyzer MS-9. (Make/Model of Analyzer: MS-9 (Mellet Schloesing). Standard chemicals and reagents supplied by company were used.

e) Statistical Analysis

All data was analyzed by applying One way ANOVA with the *p value* limits of 0.05. Software used for the purpose was PRISM.

III. Results

The result of this study, on the effect of oral dosing of CAP on the hematological parameters in rats is presented in Table 1 and 2. The results showed that the hemoglobin (Hgb), Red Blood Cells (RBC) count, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC) obtained for rats administered with CAP orally were significantly ($p<0.05$) lower in a dose-dependent pattern, compared to the control (Tables 1 and 2). On the contrary, the total White Blood Cells (WBC), platelets and Hematocrit (Hct) levels obtained for rats administered with CAP orally following the same pattern, were significantly ($p<0.05$) higher, compared to the control.

Table 1 : Initial Hematological Profile of CF rats

Gp	Treatment	Hgb	RBC	Hct	MCV	MCHC	WBC	Platelets
Gp. I	Control, D.W.	11.88±0.51	7.09±0.54	44.44±2.68	62.80±2.29	26.70±0.67	7.02±1.15	530.00±112.84
Gp. II	750 mg/g b.wt	12.30±0.51	6.97±0.69	46.22±5.57	66.28±3.87	26.78±2.64	9.93±2.05	331.00±145.74
Gp. III	1500 mg/kg b.wt	12.92±0.26	7.81±0.75	52.18±3.44	66.96±2.88	24.74±1.13	10.70±2.79	339.00±162.06
Gp. IV	2250 mg/kg b.wt	12.52±0.63	7.65±0.68	48.82±3.99	63.88±1.65	23.98±5.35	10.40±3.60	391.00±52.72

Data are presented as Mean±S.D., n=5, $p< 0.05$ compared to control.

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Table 2 : Hematological Profile of CF rats after oral administration of Chloramphenicol for 24 days

Gp	Treatment	Hgb	RBC	Hct	MCV	MCHC	WBC	Platelets
Gp. I	Control, D.W.	10.42±0.30	6.96±0.38	50.48±2.53	56.42±2.27	24.62±1.39	17.94±3.62	560.20±126.80
Gp. II	750 mg/kg b.wt	11.62±0.57	5.67±0.57	55.82±5.14	58.48±1.73	24.98±0.92	16.92±3.81	339.40±28.38
Gp. III	1500 mg/kg b.wt	10.12±1.29	7.20±0.75	55.28±5.14	60.12±2.37	22.96±1.63	17.58±5.27	419.40±127.18
Gp. IV	2250 mg/kg b.wt	11.26±0.40	6.24±0.75	51.98±3.73	56.32±2.24	23.64±1.11	17.12±3.34	397.40±9.63

Data are presented as Mean±S.D., n=5, p< 0.05 compared to control.

IV. Discussion

Hematological profiles are known to provide important information about the internal environment of a given organism. The results of this present investigation showed that oral exposure to CAP caused a significant decrease in Hgb, RBC, MCV and MCHC, whereas increase in Hct, WBC and Platelets. Similar effects on hematological parameters have been reported for such other drugs as Chlorpyrifos (Y. Savithri et al., 2010), Thiodan 35 E.0 (A. K. Solanke and V. H. Singh 2000), Chloropharm (T. Fujitani et al., 2001), Endosulfan (N. Choudhary and S. C. Joshi, 2002) and Lindane (M. D. A. Baig, 2007) and Deltamethrin (S. H. Kowalczyk-Bronisz, et al., 1990). The hematotoxic condition may results from different mechanisms, including decrease in the rate of blood cells synthesis and/or increase in the rate of blood cells destruction. The observed decrease in RBC count, Hgb, MCH and MCHC may therefore, may assumed to be associated with retarded hemopoeisis, destruction and shrinkage of RBC.

Increase in total white blood cells and platelets, as well as increase in Hct, is also reported in this study. The increase in total white blood cells and lymphocyte observed in this work may be suggested to be due to stimulated lymphopoiesis and/or enhanced release of lymphocytes from lymph myeloid tissue (B. K. Das and S. C. Mukherjee, 2003). This lymphocyte response might be a direct stimulatory effect of toxic substances on lymphoid tissues. Alternatively, this response may be assumed to be associated with the drug induced tissue damage and disturbance of the non-specific immune system leading to increased production of leukocytes.

Researchers have reported that CAP induce and enhances some defects which results in damage to undifferentiated marrow stem cells (E. P. Cronkite, 1964). Other researchers suggested that certain enteric bacteria can produce a specific enzyme that degrades CAP to a toxic product (R. Holt, 1967). This was suggested by further studies, which suggests that the metabolites of CAP generated by intestinal bacteria undergo further metabolic transformations in system with *in situ* production of toxic intermediate (A. A. Yunis, 1989 (a)). In a study (A. A. Yunis, 1973 (b)) it was actually revealed that the p-nitrosulfathiazole group is responsible for CAP induced hematotoxicity by inhibiting DNA synthesis in marrow stem cells. This theory was based on the observation that thiamphenicol which is a CAP derivative, does not have a p-nitrosulfathiazole group and does not cause hematotoxicity and thus, extensively used in Europe. This theory was further supported by studies indicating CAP reduced to p-nitrosulfathiazole which is a short lived reduction intermediate and leads to helix destabilization and strand breakage (M. Irena, et al., 1983) except than being unstable these intermediates are highly toxic (P. Eyer, et al., 1984). At a concentration of 2000-4000 μg/ml CAP depressed phagocytosis and burst activity of neutrophils (M. J. Paape, et al., 1990). Other studies suggests that CAP directly induce apoptosis in hematopoietic stem cells, directly leading to hematotoxicity (C. I. Kong, et al., 2000).

V. Conclusion

In conclusion, significant adverse changes in hematological parameters are reported to be associated with exposure to CAP, in this present study. This therefore suggest that exposure to CAP may be considered to be among the risk factors for the development of anaemic condition. Hence, exposure to this drug should be minimized.

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