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Toxic Effects of Clindamycin-Hydrochloride in Healthy Rodents

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Systemic administration of clindamycin-hydrochloride (an antibiotic) is mainly associated with gastro-intestinal disturbances and allergic reactions. Little is known of its haematological and biochemical toxicity.
Objective: To evaluate the haematological and biochemical changes associated with indiscriminate administration of oral clindamycin-hydrochloride in clinically healthy rodents.
Materials and Methods: Twenty Wistar rats (130-189 grams) divided into four groups (A-D) of five rats each were used. Rats in group A (control) were treated with distilled water. Groups B-D received 0.2mL (below normal dose), 0.4mL (normal dose) and 1.0mL (above normal dose) of clindamycin-hydrochloride (75mg/5mL) at 8 hourly intervals, three times daily for 14 days, respectively. Thereafter, blood was collected through both ocular and cardiac puncture into ethylene diamine tetra acetic acid (EDTA) and lithium heparin bottles for evaluation of haematological and biochemical parameters, respectively.
Results: Significant ($P < 0.05$) increases in total white blood cell (WBC) counts and decreases in eosinophil (Eos) counts occurred in clindamycin-treated rats. In addition, significant ($P < 0.05$) increases in concentrations of Total cholesterol, Triglyceride and High-density lipoprotein, respectively, as well as decreases in concentrations of Albumin, Alanine transaminase and Gamma-glutamyl transpeptidase, respectively also occurred in clindamycin-treated rats.
Conclusion: Indiscriminate use of clindamycin-hydrochloride produces adverse haematological and biochemical changes in Wistar rats which may be a reflection of systemic toxicity, allergic reaction as well as liver and kidney dysfunction.

Keywords: Toxicity, Liver function, Kidney function, Wistar rats, Clindamycin-hydrochloride

INTRODUCTION

Over time, research has shown that consumption of antibiotics produces several undesirable consequences which may be categorized as pharmacological, haematological, biochemical, pathological, genotoxic as well as allergic reactions in different animal species and humans (Mshelia and Madusolumuo, 2021). In clinical practice and biomedical research, haematological and biochemical parameters are crucial in determining the diagnosis of pathologic events, either directly or indirectly as

indicators of organ function or dysfunction as well as, monitoring chemotherapeutic prognosis (Mshelia and Madusolumuo, 2021). Quite a number of studies on the impact of diverse classes of antibiotics in different animal models have been initiatedwith varied, wide-ranging and insightful outcome. Our test antibiotic (Clindamycin-hydrochloride) which is a lincosamide antibiotic has a wide spectrum of anti-bacterial activity including but not limited to, the management of septicemia; intra-abdominal, lower respiratory and gynecological infections; bone and skin related infections and a host of others (Al Khaja and Sequeira, 2021; Nagarkoti *et al*., 2021). It inhibits bacterial protein synthesis by preventing the formation of peptide bonds thus, exhibiting bacteriostatic or bacteriocidal activity depending on, the causative organism, location of infection and therapeutic dose (Park *et al*., 2019; Struzycka *et al*., 2019; Ma *et al*., 2019). Administration of appropriate doses of clindamycin in oral (capsule/solution), intramuscular as well as intravenous forms have been known to effectively manage systemic infections (Greenberg *et al*., 2020) with, side effects reported to be nausea, vomiting, diarrhea (2-20% of patients) and allergic reactions such as maculopapular skin rash (10% of patients) (Paradis *et al*., 2020). A more severe or life-threatening adverse effect (*Pseudomembranous colitis*) is caused by overgrowth of *Clostridium difficile* as a consequence of depletion of much of the gastrointestinal tract's normal flora in 0.1-10% of patients receiving clindamycin (Savaris *et al*., 2019). Owing to its wide-spectrum antibacterial activity, clindamycin is widely prescribed in medical practice and its use as with other antibiotics are also commonly abused especially in Sub-Saharan Africa and other developing countries with little information on its consequences on blood profiles. What then would be the implication of inappropriate systemic use of clindamycin. This study was therefore conceived with the aim of investigating the alterations in haematological and biochemical parameters that may be associated with experimental doses of clindamycin in clinically healthy Wistar rats. To the best of our knowledge this has not been previously reported.

METHODOLOGY

Study area and study materials

The study was conducted at the animal house of the Department of Anatomy, Babcock University, Ilishan-Remo, Ogun State, South-West of Nigeria. Twenty Wistar rats weighing between 130 and 189 grams procured from the animal house of Babcock University were acclimatized under laboratory conditions for 14 days. They were kept in wooden cages with saw dust beddings which were replaced on a daily basis. Ventilation as well as access to water and pelletized growers mash was adequate. Clindamycin-hydrochloride (Pfizer) was purchased and certified by a pharmacologist at the Babcock University Teaching Hospital (BUTH).

Study design

Subsequent to laboratory acclimatization, the rats were separated into 4 groups (A-D), consisting of 5 rats each. All rats were fed with pelletized growers mash and water ad libitum. Rats in group A did not receive clindamycin-hydrochloride treatment and served as control. Rats in groups B-D were administered with 0.2mL (below normal dose), 0.4mL (normal dose) and 1.0mL (above normal dose) of clindamycin-hydrochloride (75mg/5mL) at 8 hourly intervals three times daily by gavage, respectively. Rats in all groups were exposed to experimental conditions for 14 days. Blood was collected through ocular and cardiac puncture through the left ventricle following administration of anesthesia (Williams *et al*., 2020) into ethylene-diamine-tetraacetic acid bottles for full blood count by a quantitative automated haematology analyzer (OutroSH800 plus) and lithium heparin bottles for analysis of biochemical parameters such as Urea (Diacetyl monoxime method), Total cholesterol (Cholesterol oxidase method), Triglyceride (Colorimetric method), Low density lipoprotein (Friedewald's equation), High density lipoprotein (Colorimetric method), Total protein (TP) (Biuret method), Albumin (ALB) (Bromocresol Green dye binding method), Aspartate amino transferase (AST) (Colorimetric method), Alanine transaminase (ALT) (Colorimetric method), Alkaline phosphatase (ALP) (Colorimetric method), Total bilirubin (TB) (Jendrassik and Grof method) as well as Gamma-glutamyl transpeptidase (GGT) (Szasz, Rosalki and Tarlow method).

Statistical analysis

Results of both haematological and biochemical analyses were computed statistically using IBM SPSS version 23.0. Data was expressed as mean ± standard deviation. Analysis of variance (ANOVA) was used to check significance among means of all groups. Probability of ≤ 0.05 was considered significant.

RESULTS

Haematological analysis

Table 1 displays the results of full blood count expressed as Mean ± S.D. in rats treated with experimental doses of clindamycin-hydrochloride as well as rats in the untreated (control) group. Graphs of comparative mean for haematological indices exhibiting significant statistical difference are displayed in Figs.1a (white blood cells) and 1b (eosinophils), respectively. Generally, rats in the treated groups had higher values for; white blood cells ($P< 0.05$), lymphocytes, basophils, monocytes, mean corpuscular volume, mean corpuscular haemoglobin concentration, red cell distribution width, red cell distribution size, mean platelet volume, procalcitonin, platelet distribution width ($P> 0.05$), respectively than rats in the untreated group and lowervalues for; eosinophils ($P< 0.05$), neutrophils, red blood cells, haemoglobin, haematocrit, mean corpuscular haemoglobin and platelets ($P> 0.05$), respectively than rats in the untreated group.

Table 1: Haematological changes (as mean±SD) induced by clindamycinhydrochloride in Wistar rats

Haematological Parameters	Below normal dose (0.2mL)	Normal dose (0.4mL)	Above normal dose (1.0mL)	Control (dH_2O)	P - value
WBC	11.80±2.70	16.90±7.80	16.90±2.50	8.30±3.20	0.02*
Lymphs	64.90±9.60	69.70±4.50	69.90±3.80	58.30±10.00	0.09
Basos	0.30±0.11	0.20±0.05	0.26±0.05	0.26±0.09	0.26
Neuts	31.02±8.90	25.00±4.10	24.10±4.10	33.10±5.07	0.07
Monos	3.08±1.90	5.00±2.20	5.70±2.70	3.60±1.92	0.24
Eos	0.01±0.11	0.04±0.05	0.80±0.50	0.82±0.87	0.04*
RBC	7.00±1.36	6.90±0.76	7.50±1.09	7.70±0.67	0.49
HGB	13.70±2.50	13.20±1.30	15.20±2.30	15.86±0.80	0.12
HCT	43.40±5.70	47.00±10.70	47.80±7.10	50.80±2.70	0.46
MCV	62.20±5.10	67.90±9.70	63.80±4.30	63.00±4.30	0.63
MCH	19.26±0.18	19.30±0.68	20.30±0.32	20.60±1.30	0.07
MCHC	31.50±2.40	28.90±4.30	32.00±2.10	31.28±1.96	0.36
RCDW	23.90±3.90	24.00±4.90	19.80±0.90	21.60±2.40	0.19
RCDS	53.70±12.30	63.94±23.70	46.90±5.20	55.40±14.90	0.42
Plt	825.20±144.10	734.20±241.80	719.00±71.90	891.20±254.87	0.45
MPV	7.60±0.25	7.70±0.40	7.90±0.60	7.60±0.25	0.52
PCT	0.59±0.11	0.56±0.16	0.60±0.04	0.68±0.19	0.57
PDW	11.40±0.90	11.30±1.80	11.70±1.30	10.64±0.90	0.62

* Significant at $P \leq 0.05$

WBC=White blood cells ($10^3/\mu L$), Lymphs=Lymphocytes (%), Basos=Basophils (%), Neuts=Neutrophils (%), Monos=Monocytes (%), Eos=Eosinophils (%), RBC=Red blood cells ($10^6/\mu L$), HGB=Hemogblobin (g/dL), HCT=Hematocrit (%), MCV=Mean corpuscular volume (fL), MCH=Mean corpuscular haemoglobin (pg), MCHC=Mean corpuscular haemoglobin concentration (g/dL), RCDW=Red cell distribution width (%), RCDS=Red cell distribution size (fL), Plt=Platelets ($10^3/\mu L$), MPV=Mean platelet volume (fL), PCT=Procalcitonin (%), PDW=Platelet distribution width (%), dH_2O=Distilled water.

(a) (b)

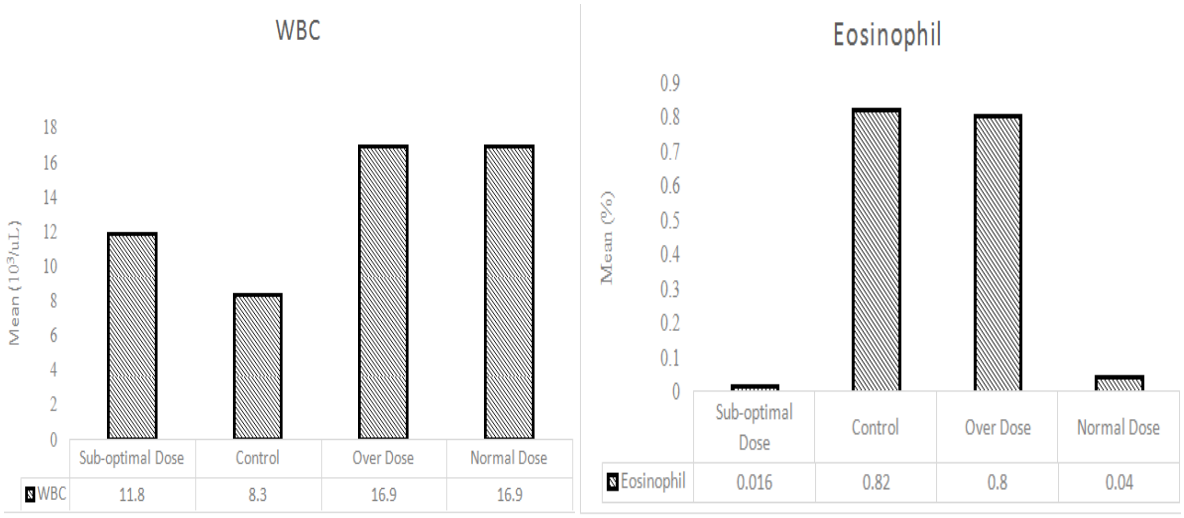

Figure 1: Graphs of mean comparison of WBC (a) and Eos (b) exhibiting significant statistical difference.

Biochemical analysis

Results of biochemical parameters analyzed in rats exposed to experimental doses of clindamycin-hydrochloride as well as rats in the untreated (control) group are expressed as Mean ± S.D. and shown in Table 2; while the plotted graphs of comparative mean of biochemical parameters exhibiting significant statistical difference are shown in Figure 2(a-f). Rats in the treated groups had higher values for; total cholesterol, triglyceride, high density lipoprotein and gamma-glutamyl transpeptidase ($P< 0.05$), respectively as well as urea, low density lipoprotein, total protein, aspartate amino transferase, alkaline phosphatase and total bilirubin ($P> 0.05$), respectively than rats in the untreated group and lower values for albumin and aspartate amino transferase ($P< 0.05$), respectively than rats in the untreated group.

Table 2: Biochemical changes (as Mean±S.D) induced by Clindamycin-hydrochloride in Wistar rats.

Biochemical parameters	Below normal dose (0.2mL)	Normal dose (0.4mL)	Above normal dose (1.0mL)	Control (dH_2O)	P - value
U	42.00±6.90	40.40±11.10	37.60±5.70	37.60±6.10	0.76
TCHOL	77.40±4.16	90.20±4.80	96.00±11.50	72.00±13.40	0.00*
TRI	45.40±13.28	162.00±90.60	172.60±78.90	74.20±50.50	0.02*
LDL	46.80±4.14	25.60±18.60	32.40±23.90	35.60±3.40	0.22
HDL	24.00±3.70	32.20±4.80	29.20±5.26	23.20±3.80	0.02*
TP	7.20±0.90	6.90±0.90	8.20±0.80	7.90±0.70	0.09
ALB	3.60±0.17	3.90±0.23	3.70±0.23	4.20±9.20	0.00*
AST	119.80±18.10	118.60±17.40	109.60±17.90	108.20±32.60	0.79
ALT	33.80±3.30	35.60±13.80	41.20±6.80	57.20±14.90	0.01*
ALP	120.60±20.40	179.60±36.80	149.20±50.80	152.80±4.80	0.08
TB	0.41±0.13	0.46±0.20	0.50±0.16	0.44±0.03	0.73
GGT	29.00±5.40	44.00±7.50	38.80±10.80	40.20±0.84	0.03*

* Significant at $P \leq 0.05$.

Keys**:** U=Urea (mg/dL),TCHOL=Total cholesterol (mg/dL), TRI=Triglyceride (mg/dL), LDL=Low density cholesterol (mg/dL), HDL=High density cholesterol (mg/dL), TP=Total protein (mg/dL), ALB=Albumin (mg/dL), AST=Aspartate amino transferase (IU/L), ALT=Alanine transaminase (IU/L), ALP=Alkaline phosphatase (IU/L), TB=Total bilirubin (mg/dL), GGT=Gamma-glutamyl transferase (IU/L), dH_2O= Distilled water.

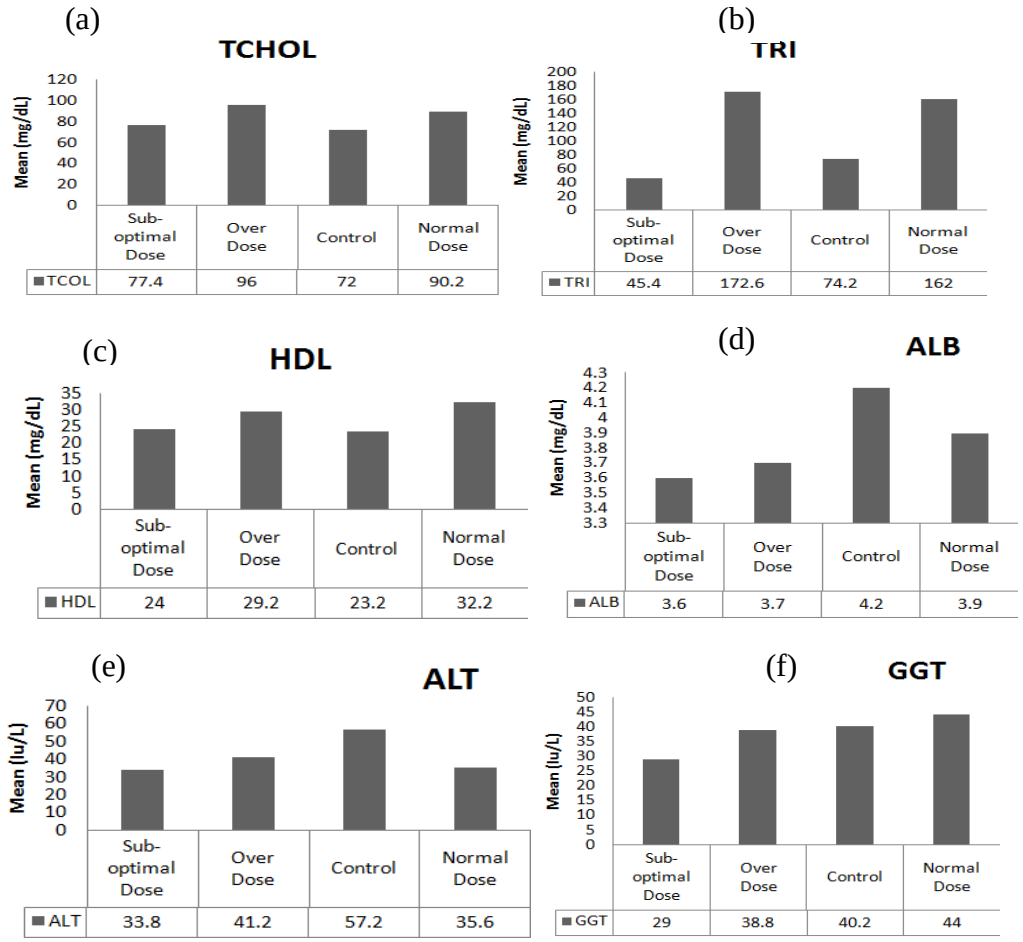

Figure 2: Mean comparison of (a) TCHOL; (b) TRI; (c) HDL; (d) ALB; (e) ALT and (f) GGT exhibiting significant statistical difference.

DISCUSSION

Non-compliance to prescribed medication dosage regimen in the form of below and above recommended dosages is a challenge that is pervasive in human society with possible adverse toxicological effects (Gast and Mathes, 2019). Haematological and biochemical studies constitute a cardinal tool for evaluating such toxicological consequences of drugs in animal and human systems (Corum *et al*., 2022). In addition, the first line of approach in determining liver and kidney function in the laboratory is the evaluation of several parameters including but not limited to U, TCHOL, TRI, LDL, HDL, TP, ALB, AST, ALT, ALP, TB and GGT (Lv *et al*., 2021; Nunes *et al*., 2022).

Hence, this study evaluated the effect of indiscriminate doses of oral clindamycin-hydrochloride (an antibiotic) on haematological as well as biochemical parameters using clinically healthy Wistar rats as model. A large number of results from previous studies have shown that, administration of sundry antibiotics yielded quantifiable alterations in haematological parameters in different animal models. Among these studies, cefquinome produced insignificant decreases in WBC, RBC, HGB, HCT and Plt in clinically healthy Merino sheep (Corum *et al*., 2022); diminazene aceturate (alone) and diminazene aceturate (plus oxytetracycline) treatments produced significantly

reduced HCT, HGB and RBC in non-morbid dogs indigenous to Nigeria (Onyeachonam *et al*., 2022); oxytetracycline and gentamicin produced non-significant decreases in HCT, HGB, MCV, MCH, WBC, Lymphs, Monos as well as increases in RBC, MCHC and Neuts in *Cyprinus carpio* juveniles (Kondera *et al*., 2020); sulfamethoxazole produced significant increase in WBC as well as decreases in HGB, Plt and RBC in *Cyprinus carpio* (Iftikhar and Hashmi, 2021); ceftriazone treatment caused significant increases in HCT, MCV, WBC, Neuts, Lymphs, Eos and Monos as well as decreases in HGB, RBC and MCH in albino rats (Mshelia and Madusolumuo, 2021); enrofloxacin led to non-significant decreases in RBC, HGB and HCT (Bhuiyan *et al*., 2021). In our study, aside from observing several post-treatment changes in haematological parameters in the healthy Wistar rats used which agrees with the studies enumerated above, we particularly observed significant increases and decreases in the values of WBC (leucocytosis) and Eos (eosinopenia), respectively in the treated rats. The observed changes in our study are suggestive of an inflammatory process in response to allergic reaction.

Several post-treatment changes in biochemical parameters were also observed in rats exposed to clindamycin-hydrochloride in our study.TCHOL was significantly increased. Conditions known to cause such elevated TCHOL concentration include nephrosis and nephrotic syndrome. Several studies in humans have shown that dyslipidemia which include elevated values of TCHOL is a risk factor not only for the onset but, also for the progression of chronic kidney disease (Miao *et al*., 2021; Weldegiorgis and Woodward, 2022). The concentration of TRI was also observed to be commonly elevated. It is believed that many of the clinical conditions that cause an increase in cholesterol levels also cause increase in TRI level. Thus, increased TRI level is a common feature in liver disease and nephrotic syndrome. As with TCHOL, several studies in humans have shown TRI to be a risk factor for onset and progression of chronic kidney disease (Miao *et al*., 2021; Huang *et al*., 2021; Weldegiorgis and Woodward, 2022) as well as for pathologic liver conditions such as hepatic steatosis, hepatomegaly and non-alcoholic fatty liver disease (Xing *et al*., 2021; Heeren and Scheja, 2021; Kathak *et al*., 2022). The level of HDL was also observed to be for the most part, significantly higher. Increased value of HDL is known to correlate positively with chronic liver disease. This is substantiated by McCullough *et al*., (2019) who reported a high level of HDL in patients with nonalcoholic fatty liver disease. ALB concentration was observed to be commonly significantly lower. Clinical conditions that have been associated with hypoalbuminemia include acute hepatitis and chronic liver disease as a result of reduced synthesis; nephrotic syndrome as a result of increased loss. A particular report by Carvalho and Machado, (2018) has shown that decreased plasmatic albumin concentration is linked with advanced liver cirrhosis. While, Alves *et al*., (2018) reported that low serum albumin concentration is associated with the high mortality rate recorded in end state kidney disease patients, Lang *et al*., (2018) reported an association between low serum albumin levels and kidney function decline and chronic kidney disease. In the same vein, Huang *et al*., (2022) reported an association between low blood albumin concentration and mortality risk in patients with chronic kidney disease. The activity of ALT was also significantly lower. Clinically, increased levels are associated but not restricted to hepatocellular disease, active cirrhosis, toxic hepatitis, liver congestion, hepatic injury in myocardial infarction and chronic active hepatitis. The report of Park *et al*., (2019) indicated that ALT activity below a particular limit is a positive predictor of poor liver outcomes. This therefore agrees with our result. Activity of GGT was also found to be significantly higher. The studies conducted by Shibabaw *et al*., (2019) had reported similar increases in the activity of GGT thereby, corroborating our result. Such enhanced values of GGT are associated with cirrhosis of the liver.

CONCLUSION

The double challenge of rising prevalence in liver and kidney diseases coupled with unmitigated access as well as inappropriate use of drugs particularly antibiotics among citizens of developing countries especially those in Sub-Saharan Africa is now a growing source of concern. This study suggests that systemically administered clindamycin-hydrochloride across different experimental doses could lead to undesirable effects. Inflammatory process was observed as well as changes indicating dysfunctions of the liver and kidney, suggesting that inappropriate use of clindamycin-hydrochloride has a likelihood of inducing allergic reaction as well as liver and kidney damage.

ETHICAL CONSIDERATION

Ethical approval (NHREC/24/01/2020; BUHREC 303/22) for the use and sacrifice of experimental animals was obtained from the Babcock University Health Research Ethics Committee (BUHREC).

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