Medical and Pharmaceutical Journal

Volume 3 Issue 1

Med. Pharm. J. Original article

Metronidazole Induced Neurotoxicity: Possible Central Serotonergic and Noradrenergic System Involvement

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DOI: 10.55940/medphar202474
Submitted: 28-Jan-2024
Accepted: 30- Mar -2024
Published:15-April-2024

Abstract

Background: Metronidazole is a synthetic 5-nitroimidazole antibiotic. It remains a first-line therapy for anaerobic, parasitic, and bacterial infections in human and veterinary medicine. However, Metronidazole-induced neurotoxicity is a rising challenge. The mechanism of neurotoxicity induction is still unknown.

Objective: To investigate a possible interference of metronidazole with central monoaminergic mechanisms using the Forced Swim Test.

Methods: sixty adult rats were divided into 10 groups (n=10 for metronidazole and saline, n=5 for other groups). Group 1 = 5 ml/kg normal saline; Group 2 = 50 mg/kg metronidazole; group 3= 15 mg/kg imipramine; Group 4 =15 mg/kg imipramine + 50 mg/kg metronidazole. Group 5 = 5 mg/kg fluoxetine; Group 6 received 5 mg/kg fluoxetine + 50 mg/kg metronidazole; Group 7 = labetalol 10 mg/kg; Groups 8, 9 and 10 received labetalol 10 mg/kg + 50 mg/kg metronidazole, PCPA (p-chlorophenylalanine) 100 mg/kg and PCPA 100 mg/kg + 50 mg/kg metronidazole daily X 28 days. On day 28, FST was done 1h after the respective treatments. On day 29, blood samples were collected under halothane anesthesia for hematological assessment.

Results: Immobility time increased ($P<0.01$) in the groups treated with metronidazole, labetalol, PCPA, labetalol + metronidazole, and PCPA+ metronidazole. Swimming was reduced by metronidazole, PCPA, metronidazole + PCPA and metronidazole + labetalol. Metronidazole + labetalol reduced climbing. These effects were not reduced by co-treatment with imipramine or fluoxetine. White blood cell count increased ($p<0.01$) in all treatment groups. Lymphocyte percent increased in the metronidazole-treated groups.

Conclusion: Interference with postsynaptic central monoaminergic neurotransmission and immunomodulation may contribute to metronidazole-induced neurotoxicity.

Keywords: Antibiomania, Antidepressants, depression, metronidazole , Neurotoxicity, neurotransmission.

INTRODUCTION

Metronidazole is a synthetic 5-nitroimidazole antibiotic. It remains a first-line therapy for anaerobic, parasitic as well as bacterial infections in human and veterinary medicine ever since its development in 1959 [1]. Apart from being categorized as an anti-protozoal and anti-bactericidal drug, metronidazole possesses some immuno-modulatory properties and is employed in the treatment of inflammatory bowel disease (IBD) in both dogs and cats [2]. Metronidazole is inexpensive with an undiminished antimicrobial activity and clinical profile [3]; However, its use has been associated with several neuropsychiatric side effects [4]. Metronidazole-induced neurotoxicity is rare but can manifest as several neurologic syndromes, including but not limited to peripheral or central neuropathy, depression and mania [5], dizziness, vertigo, headache, and encephalopathy collectively referred to as metronidazole-induced neurotoxicity [6].

In recent times, there have been rising reports of neurotoxicity resulting from the use of metronidazole in humans. Most cases were from the United States and Korea, and a few more from India, Japan, Australia, Canada, United Kingdom, Belgium, Chile, Germany, Israel, Netherlands, Nigeria, Taiwan, Tunisia, and Turkey [7].

The mechanism of metronidazole-induced neurotoxicity remains sketchy, although several hypotheses have been proposed by various researchers [8]. A review of the literature reveals several cases of metronidazole-induced depression [9,10]. This study was designed to investigate the relationship between metronidazole-induced neurotoxicity and noradrenergic and serotonergic mechanisms using the forced swim test.

MATERIALS AND METHODS

Metronidazole, fluoxetine, p-chlorophenylalanine (PCPA), Labetalol and Imipramine (Sigma, St. Louis, MO, USA) were obtained from Rovet chemicals Edo State. Stock solutions of metronidazole, PCPA, labetalol, and imipramine were suspended in 0.5% Tween-80. All other reagents and chemicals used were of analytical grade and were obtained from reputable companies.

Animals

Sixty apparently healthy adult Wister rats of both sexes weighing between 150 and 200 g were used for this study and were obtained from the animal breeding and research unit of the institution. The animals were housed in twelve (12) different cages, with separate cages for males and females (maximum of 5 rats per cage) to avoid overcrowding. The animals were maintained on standard rodent chow (Livestock Feeds, Edo, Nigeria) and had free access to water. All animals were handled per standard protocols prescribed by the National Research Council, 2011,11 and ARRIVE 2.0 guidelines for handling animals (https://arriveguidelines.org/arrive-guidelines/sample-size) following institutional ethical approval.

Experimental Protocol

Adult rats were divided into 10 groups (n=10 for 0.9% saline (Control) and metronidazole, n=5 for other treatments).

Group 1 was given 5 ml/kg 0.9% saline, Group 2 received 50 mg/kg metronidazole, 15 mg/kg imipramine was given to Group 3, and Group 4 received 15 mg/kg Imipramine + 50 mg/kg metronidazole. Group 5 was administered 5 mg/kg fluoxetine, Group 6 received 5 mg/kg fluoxetine + 50 mg/kg metronidazole and group 7 was given labetalol 10 mg/kg. Groups 8, 9 and 10 received labetalol 10 mg/kg + 50 mg/kg metronidazole, PCPA 100 mg/kg and PCPA 100 mg/kg + 50 mg/kg metronidazole respectively. The drugs were administered daily via an oral gavage needle for 28 days, metronidazole, fluoxetine, PCPA and labetalol were solubilized with 0.5% tween-80. The treatment groups were divided into two broad groups: the groups with fluoxetine and PCPA were used for evaluation of serotonergic mechanism and were grouped together as Group A; while groups with labetalol and imipramine were used for the evaluation of the noradrenergic mechanism and were referred to collectively as Group B. On the 28th day of drug administration, the forced swim test was carried out 1 hour after administration of the daily drug dose. On the 29th day, blood samples were collected under halothane anesthesia for hematological assessment.

Forced Swim Test (modified)

The method of Porsolt *et al*., 1977 [12], and modified by Detke *et al*., (1995) [13] was applied to evaluate the effect of the various treatments on the animals. Briefly, an open cylindrical container of 25 cm diameter and 60 cm height, filled with water at 25 ± 1°C to a depth of 25 cm was used in this experiment, which was performed without noise interference. One (1) hour after the daily drug dose, each rat was exposed to the forced swim test in the cylinder. Parameters such as duration of immobility, swimming, and climbing activities were recorded for 5 min within a 6 min test. After this, the rat was removed from the swimming tank, towel dried, and transferred to its home cage.

Hematological Analysis

Blood was collected from the rat abdominal aorta under halothane anesthesia using a 2 ml syringe and transferred into anticoagulant (EDTA) tubes and later processed according to manufacturer's instructions in an automated system ((sysmex hematology coagulation system®, modelkx-21N. Sysmex Incorporation Kobe, Japan). The parameters measured include white blood cell count (WBC), red blood cells (RBC), hemoglobin concentration (Hb), platelets count (PLT), Neutrophil (NEU), and Lymphocyte percent (LYM).

Statistical Analysis

Results are expressed as mean ± standard error of the mean (SEM) and "n" is the number of animals per group. The statistical method used was one-way ANOVA followed by Dunnet's post hoc test for multiple comparisons (GraphPad Prism 6 Software, San Diego, California, USA). Statistical differences between the compared data were considered significant at $p<0.05$.

RESULTS

Effect of 28 days of drug treatment on the forced swim test in group A rats

Figure 1 shows that in category A, all treatment groups except the fluoxetine-treated group increased (P<0.01) the immobility time and reduced swimming activity in rats subjected to the forced swim test (FST) while fluoxetine treatment reduced the immobility time and increased (P<0.01) swimming activity in rats compared to control. The fluoxetine-treated group had increased swimming and reduced immobility time (P<0.01) compared to the metronidazole-only group. Co-treatment with fluoxetine did not reverse the increase in immobility time and reduction in swimming activity induced by metronidazole in treated rats.

Effect of 28 days of drug treatment on the forced swim test in group B rats

In category B (Figure 2), except for the imipramine group, immobility time increased significantly (P<0.01) in all others when compared to the control. The imipramine-treated group had lower (P<0.01) immobility time compared to the metronidazole-only treated group. Swimming activity reduced (P<0.05) in the metronidazole and metronidazole + labetalol treated groups compared to the control. Climbing activity increased significantly in the imipramine-treated group and was reduced in the metronidazole + labetalol and metronidazole + imipramine-treated groups compared to the control group (Figure 2).

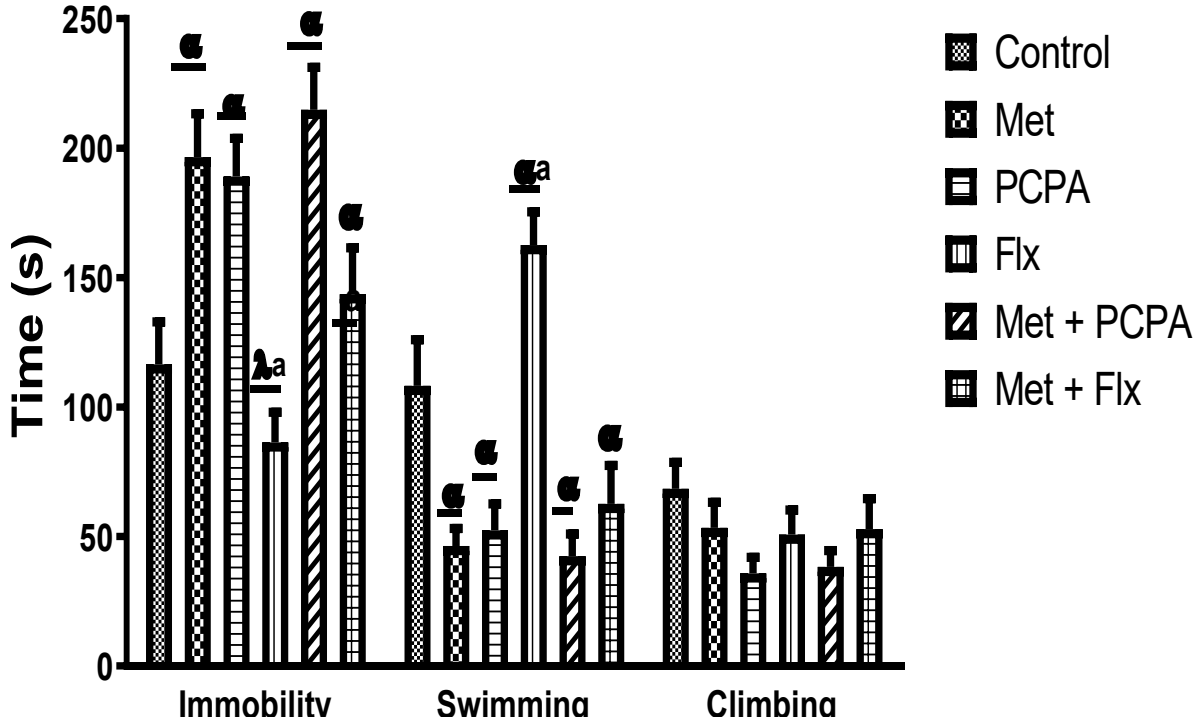

Figure 1: Effect of daily oral metronidazole treatment for 28 days on serotoninergic mechanism in depression. n=5, $^{\alpha}P$<0.001, $^{\lambda}P$<0.05 compared to control. ^{a}P<0.01, compared to metronidazole only. Met: metronidazole (50 mg/kg), PCPA: p-chlorophenylalanine (100 mg/kg), Flx: fluoxetine (5 mg/kg), met (50 mg/kg) + PCPA (100 mg/kg), met (50 mg/kg) + Flx (5 mg/kg), control (5 ml/kg 0.5% Tween-80®).

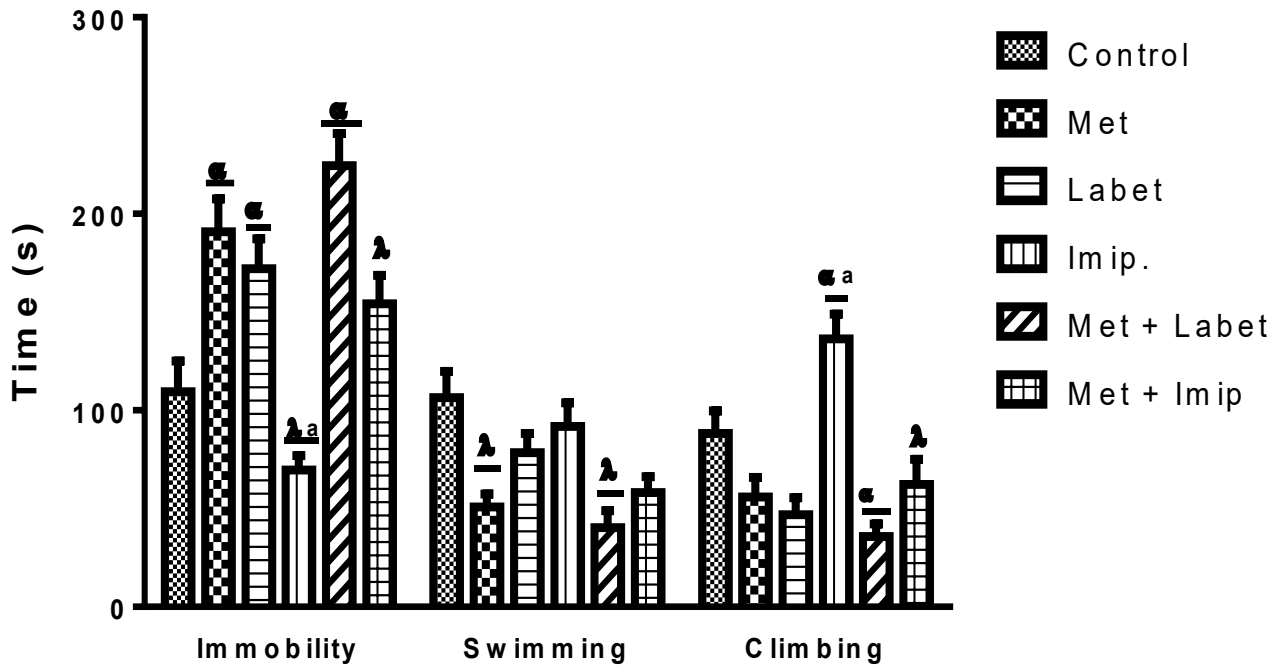

Figure 2: Effect of 28 days of oral treatment on the noradrenergic mechanism of depression. n=5, $^{\alpha}P<0.001$, $^{\lambda}P<0.05$ compared to control. $^{a}P<0.001$, $^{b}P<0.05$ compared to metronidazole only. Met: metronidazole (50 mg/kg), Labet: labetalol (10 mg/kg), Imip: imipramine (15 mg/kg), met (50 mg/kg) + labet (10 mg/kg), met (50 mg/kg) + Imip (15 mg/kg), control (5 ml/kg 0.5% Tween-80®)

Effect of various treatments on haematological indices of treated rats

Table 1 shows the effect of metronidazole on the hematological indices of treated rats (×28 days) in group A. Lymphocyte percent was elevated (*P<0.01*) in the metronidazole-treated rats compared with control. WBC count increased (*P<0.01*) in the metronidazole alone, metronidazole + PCPA, and metronidazole + fluoxetine treated groups compared to control.

The effect of treatment on the haematologic parameters of rats in the noradrenergic mechanism group is shown in Table 2. WBC increased in all treatment groups compared to control, but only the labetalol and metronidazole + labetalol group increased (*P<0.001*) compared to metronidazole. Lymphocyte percent increased in the metronidazole-only treated group compared with control.

Table 1: Effect of daily (×28 days) dosing with metronidazole and typical agents that affect serotonergic mechanisms on haematological parameters in rats.

Parameter	Control	Metronidazole	PCPA	Fluoxetine	Met + PCPA	Met + Flx
PLT ($\times10^6$/µl)	818.6±40.44	820.8 ± 52.83	808.4±38.13	822.6±43.40	820.2±17.91	805.8±48.52
WBC ($\times10^6$/µl)	8.4±0.31	14.6±0.45*	9.7±0.81	8.1±0.25	12.6±0.94*	13.8±0.67*
RBC ($\times10^6$/µl)	6.7±0.33	6.3±0.34	6.2±0.32	7.2±0.54	6.2±0.22	6.8±0.22
LYM (%)	46.4±1.93	59.60 ± 1.48**	50.2±1.80	53.1±2.44	51.8±2.13	53.2±4.52
NEU (%)	39.0±0.32	39.4±1.78	38.4±0.41	35.2±1.68	35.2±2.13	37.2±2.18
HB (g/dl)	12.2±0.33	12.7±0.38	12.6±0.44	12.4±0.66	12.3±0.44	11.9±0.82

PLT = Platelets; WBC = White Blood Cells; RBC = Red Blood Cells; LYM = Lymphocytes; NEU = Neutrophils; HB = Haemoglobin. Met- metronidazole, PCPA= p-chlorophenylalanine, Flx-fluoxetine n=5; *= p< 0.05, **=p<0.01 compared to control.

Table 2: Effect of daily (×28 days) oral treatment of metronidazole and typical agents that affect noradrenergic mechanisms on haematological parameters.

Parameter	Control	Metronidazole	Imipramine	Labetalol	Met + Imip	Met + Labet
PLT ($\times10^6$/µl)	800.4±24.24	826.2 ± 30.43	792.4±28.88	802.6±33.44	810.2±24.81	815.8±38.22
WBC ($\times10^6$/µl)	8.8±0.34	11.2±0.45*	13.2±0.24**	16.8±0.26**	11.8±0.84*	15.8±0.77*
RBC ($\times10^6$/µl)	7.2±0.16	6.9±0.34	6.9±0.42	7.0±0.54	6.6±0.23	7.3±0.22
LYM (%)	47.2±2.66	57.4±1.98*	44.2±2.24	50.0±2.12	49.6±2.13	51.2±2.52
NEU (%)	37.9±1.30	52.4±1.64	38.6±1.46	44.0±1.58	42.6±2.23	49.2±2.30

HB (g/dl)	12.9±0.43	12.3±0.18	12.2±0.58	12.3±0.16	12.2±0.44	11.9±0.12

PLT = Platelets; WBC = White Blood Cells; RBC = Red Blood Cells; LYM = Lymphocytes; NEU = Neutrophils; HB = Haemoglobin. Met- metronidazole, PCPA= p-chlorophenylalanine, Flx-fluoxetine . n=5; *= p< 0.05, **=p<0.01 compared to control.

DISCUSSION

The mechanism by which metronidazole induces neurotoxicity is still a topic of debate with several proposed mechanisms, including the breakage of neuronal RNA [14], impairment of protein synthesis with resultant reversible axonal swelling and commensurate damage to the cerebellar nuclei [15-17]. Bahn, *et al.,* study that conducted in 2010 suggests a modulation of inhibitory neurotransmission by metronidazole [4]. In this study, we investigated a possible involvement of noradrenergic and serotonergic systems in metronidazole-induced neurotoxicity using the forced swim test in rats.

The forced swim test is a neuro-behavioral animal model for assessing antidepressant-like effects of drugs and chemicals [12]. The test scores the length of time the test animal spends floating idly (immobility), an increase in immobility which is an index associated with a state of misery or despair, as with clinical depression mainly results from substances with pro-depressant activity [12,18].

Depletion of noradrenaline and serotonin concentration in the central nervous system is known to play a major part in the pathophysiology of depression.[19] To explore the monoamine theory of depression, some parameters (swimming and climbing activity) were introduced as a modification of the forced swim test to distinguish between serotonergic and noradrenergic mechanisms [13]. Selective augmentation of central noradrenergic neurotransmission increases climbing activity while selective augmentation of the serotonergic pathway increases swimming activity in the forced swim test [20,21].

To establish the effect of metronidazole on the serotonergic and noradrenergic mechanisms of depression, PCPA and labetalol were used to disrupt the central serotonergic and noradrenergic pathways respectively.

P-chlorophenylalanine, an established inhibitor of tryptophan, hydroxylase is known to cause depletion of 5-HT levels [22], resulting in various neuro-cognitive deficitsand depression-like behaviour in animal models [23-26].

In this study, PCPA administered singly or in combination with metronidazole increased the immobility time and reduced swimming activity in the test animals which was comparable to the effect produced by metronidazole alone. This behavior is akin to a state of despair and suggestive of depression-like behavior.[18, 27, 26] Interestingly, the effect of metronidazole on immobility and

swimming activity was not reversed by co-administration with fluoxetine, a selective serotonin reuptake inhibitor that mediates the reuptake of serotonin into the presynaptic terminal, thus enhancing and prolonging serotonergic neurotransmission [28].

This infers that metronidazole does not directly inhibit the serotonin transporter (SERT) but may have effect on postsynaptic mechanisms that alter serotonergic transmission to induce depression-like behavior in the treated rats.

Labetalol is a dual alpha (α_1) and non-selective beta (β_1 and β_2) reversible adrenergic receptor inhibitor that competitively displaces catecholamines from these adrenoceptors [29,30].

In the central nervous system, it produces several neuro-cognitive deficits including, hallucinations, insomnia and depression [31].

Metronidazole administered alone and in combination with labetalol produced depression-like effects in the treated rats by reducing climbing and swimming activity and increasing immobility time. The tricyclic antidepressant (TCA), imipramine, which owes its antidepressant activity primarily to inhibition of noradrenaline reuptake when administered together with metronidazole, also did not reverse the effects induced by metronidazole administration [32].

Again, this suggests that the induction of depression-like effects in the metronidazole-treated rats may not be directly related to altered transmitter reuptake but modulation of postsynaptic effects.

There is currently a growing school of thought that a functional deficiency in monoaminergic transmission alone is not sufficient to account for the etiology of depression [33]. Several mechanisms have been implicated as contributing factors, including the central monoaminergic systems, the immune system, genetic factors, biological molecules (neurotrophins), and the endocrine system [34,35].

The results from the forced swim test demonstrate that induction of depression-like effects in metronidazole treated rats occurs independent of direct central monoaminergic transmitter reuptake and may involve other mechanisms.

Constituents of the blood are affected by most drugs; the counts and concentrations are sensitive indices of toxic or pathological conditions. Hematological analysis following drug administration in toxicological studies reveals the health status of the participants [36].

White blood cells are defensive cells activated in acute inflammatory conditions or tissue invasion by foreign substances [37].

Lymphocytes are major determinants of the immune status of individuals in addition to other cell subtypes found in peripheral blood [38]. The increase in the lymphocyte and white blood cell count in this study is in agreement with some other studies [39]. Another study reports that metronidazole and its hydroxyl metabolites blocked the inhibitory effect of histamine on lymphocyte proliferation in a dose-dependent fashion by increasing the mitogenic response to phytohemagglutinin resulting in an increase in the rate of lymphocyte

proliferation and hence indicating a possible immunostimulatory effect in patients after treatment with metronidazole [40]. In contrast, concentration-dependent inhibition of human peripheral blood lymphocyte proliferation, which indicates a possible immunosuppressive action, has also been reported [41]. This is thought to be due to chromosomal aberrations and DNA breakage leading to apoptosis [42].

Furthermore, the immune system is known to play a vital role in several neuropsychiatric disorders, including depression [43]. Increased levels of inflammatory molecules evidenced by elevated proinflammatory cytokines levels, cytokine receptors, chemokines, and soluble adhesion molecules have been reported in the peripheral blood and CSF of clinically depressed patients [44,45]. Cytokines are small protein molecules such as interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α) secreted by T-lymphocytes which play a great role in intercellular communications and immunomodulation [46].

Peripheral inflammatory markers affect the state of immune activation in the CNS, which, in turn, impacts explicit behavior, and can also serve as a biological index for antidepressant therapy [44, 47].

Antidepressants have been reported to significantly reduce the level of peripheral IL-6, TNF-α, and IL-10, suggesting that antidepressants may reduce the markers of peripheral inflammation [48].

An imbalance between proinflammatory and anti-inflammatory cytokines may contribute to the pathophysiology of depression [34,35].

Metronidazole at a dose of 28 mg/kg reportedly induced atrophy in the medulla of the thymus, suggesting a possible effect on the activation and differentiation of the T-lymphocytes [41], an effect that might explain the relative increase in the circulating lymphocytes. The increase in the percentage of circulating lymphocytes and white blood cell counts seen in this study may be due to an immune response to metronidazole, which may also contribute to the depression-like behavior of the treated rats.

CONCLUSION

Neurotoxicity arising from the use of metronidazole is a concern in clinical practice. Unraveling the mechanism of metronidazole-induced neurotoxicity is necessary to prevent injury and maximize therapy. In this study, metronidazole induced depression-like behavior in the treated animals and also induced immunological reactions that may contribute to its neurotoxic effects. We conclude that, metronidazole-induced neurotoxicity may arise from its interference with postsynaptic central monoaminergic neurotransmission and immunomodulation; however, this may not be its only mechanism, and as such, further research is required.

Abbreviations

PLT: Platelets; WBC: White Blood Cells; RBC: Red Blood Cells; LYM: Lymphocytes; NEU: Neutrophils; MCV: Mean Corpuscular Volume; HB: Hemoglobin; RNA: Ribonucleic acid; PCPA: P-chlorophenylalanine; TCA: Tricyclic antidepressant; IBD: inflammatory bowel disease; CNS: Central nervous system; 5-HT: 5-hydroxytryptamine; EDTA: Ethylene

diamine tetraacetic acid; SERT: Serotonin transporter

ACKNOWLEDGEMENTS

All persons who contributed substantially to the manuscript have been listed, and none has been omitted.

Funding

MW**B** is a TERTIARY EDUCATION TRUST FUND (TET Fund Scholar)

Availability of data and materials

All data collected during this study are included in this manuscript.

Consent for publication

All authors listed in the manuscript consented to publication.

Author contributions

MW**B** conceptualized and designed the experiments and conducted the statistical analysis. K**I,** DJ**B**, and MW**B** performed a literature search, conducted the experiments in parts, collected data, and prepared the manuscript in sections. K**I** and DJ**B** edited the manuscript. MW**B,** K**I**, and DJ**B** reviewed the manuscript.

Competing interests

Nil.

Ethical approval

Ethical approval (NDU/PHARM/PCO/AEC/56) was obtained from the institutional animal and ethics committee.

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How to cite this article:
Bariweni MW., **Kamenebali** I., **Bedford** DJ. Metronidazole Induced Neurotoxicity: Possible Central Serotonergic and Noradrenergic System Involvement. Med. Pharm. J. 2024;3(1):22- 34.
DOI: 10.55940/medphar202474
Available from: http://pharmacoj.com/ojs/index.php/Medph/article/view/74