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The hematological effects of vitamin B12 supplementation in rabbits treated with ivermectin: A physiological and comparative study

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Abstract
The effects of repeated ivermectin therapy on several hematological parameters were evaluated in rabbit blood. The experimental animals were randomly allocated into three groups. The first group received no medication (control group), the sec-ond was given an acceptable therapeutic dose of ivermectin (0.24 mg/kg, subcutane-ously) weekly for 30 days, and the third group received the same dose of ivermectin and intramuscular injections of vitamin B12 (1000 µg/week). Following blood col-lection, the blood samples were treated to anticoagulation using ethylenediaminetet-raacetic acid (EDTA) and utilized to assess hematological parameters. The group treated exclusively with ivermectin exhibited a statistically significant reduction ($P < 0.05$) in several hematological parameters, including total white blood cells, lymphocytes, red blood cells, platelets, and mean corpuscular hemoglobin concentration (MCHC), when compared to the control group. In contrast, other parameters-such as granulocyte count, mean absolute count, hemoglobin (HGB), packed cell volume (PCV), mean corpuscular hemoglobin (MCH), and plateletcrit (PCT)-showed no statistically significant elevations. Interestingly, the group that received vitamin B12 along with ivermectin exhibited partial improvement in several hematological parameters. Notably, levels of red blood cells, hemoglobin, and MCHC were moderately elevated compared to the ivermectin-only group, suggesting a possible protective or restorative effect of vit-amin B12 on erythropoiesis and general hematological balance. We discovered that ivermectin has a deleterious impact on hematological indicators in rabbits treated with repeated therapeutic doses over a short period of time; however, the co-administration of vitamin B12 may mitigate some of these adverse effects. There-fore, either a single ivermectin dose over extended intervals or its combination with hematopoietic-supportive agents like vitamin B12 is recommended.

Keywords: Ivermectin, red blood cells. Vit B12, White blood cells

Introduction
Ivermectin is a macrocyclic lactone produced by Streptomyces avermitilis. It is effective against a variety of internal in addition to external parasites at extremely low levels, which is why it is called a macrolide endectocide. It is widely used in farm animals and pets, in addition to being an antiparasitic agent (Chable-Bessia *et al*., 2022) [5]. It improves skin health. Recently, ivermectin has been used for treating various para-sitic infections and COVID-19 viral infections in humans (Shubnikova *et al*., 2022) [18].

According to Õmura and Crump (2004) [12], ivermectin exhibits a pharmacological potency that surpasses most current veterinary drugs, demonstrating an efficacy approximately 20-fold higher. Its primary mechanism involves acting as an agonist on chloride ion channels located in neuronal and muscular membranes, thereby increasing their permeability (Chhaiya *et al*., 2012) [7]. This enhanced permeability leads to a reduction in membrane input resistance, which in turn lowers the likelihood of initiating action potentials. Moreover, ivermectin modulates a variety of ligand-gated ion channels, including those gated by gamma-aminobutyric acid (GABA) and glutamate (GluCl), both of which are inhibitory. Through this modulation, the drug amplifies inhibitory neurotransmission pathways in invertebrates and, potentially, in the host organism as well (Taylor-Wells *et al*., 2018) [19].

In male rats, administration of both standard and elevated therapeutic doses of ivermectin led to a marked decline in sperm count and motility. Additionally, histopathological examinations revealed notable damage in vital organs such as the liver, kidneys, and testes-manifested by vascular congestion and degenerative alterations, including vacuolar and hydropic changes,

and in some cases, tissue necrosis. These structural abnormalities were further reflected in significant impairments in liver and kidney function indicators (GabAllh *et al*., 2017) [8].

Vitamin B12 (cobalamin) is a water-soluble vitamin that plays a vital role in hema-topoiesis, neurological function, and DNA synthesis. It is essential for the normal formation of red blood cells and for maintaining healthy nerve tissue. A deficiency in vitamin B12 can lead to megaloblastic anemia and neurological impairments (O'Leary & Samman, 2010) [13]. In animal models, supplementation with vitamin B12 has been associated with improved erythropoiesis, immune modulation, and reduced oxidative stress. Given its role in supporting hematological health, vitamin B12 is hypothesized to mitigate the adverse hematological effects induced by certain pharmacological agents, including antiparasitic drugs like ivermectin.

The present study was conducted to investigate the effect of repeated therapeutic doses of ivermectin on the complete blood count (CBC) in rabbits and to measure the potential defensive role of vitamin B12 when administered concurrently.

Material and methods

Ten adult rabbits were used in this experiment, and they were exposed to the ex-perimental conditions for two weeks to acclimate them. They were randomly sepa-rated into two groups (n=5): For four weeks, the ivermectin group was given a sub-cutaneous injection of 0.25 mg IVM/kg body weight (Arise *et al*., 2012) [12], control group: remain without treatment. After 15 and 30 days, each animal's blood was col-lected by cardiac puncture. The blood sample was anticoagulated using sodium cit-rate; According to Schalm, (2000) [17], it was used to evaluate the complete blood count, using Hemolyzer® 5 NG (open mode). All data were statistically analyzed using a Two-way anova test (SPSS category 21) to demonstrate variations among groups and times. Values were described as means± standard error at P≤0.05 (Larsen *et al*., 1973) [10].

Results

The effects of Ivermectin, B12 on hematological parameters related with white blood cells (WBC)

The results indicate a significant (P≤0.05) decrease in total white blood cell count in the treatment (ivermectin) group compared with the control group and b12 group at periods. As well as a decrease in lymphocytes, especially after 30 days. On the other hand, there is no difference in the mid-range of absolute numbers.

Table 1: The effects of Ivermectin on hematological parameters related with white blood cells in rabbits.

Parameters	Control	Ivermectin	B12	Ivermactin +b12	LSD
White blood cells (10^9/l)	11.1±0.53 Aa	5.4 ±0.1 Cc	12.1±0.43 Aa	9.3 ±0.1 Bb	1.43
	11.3 ±0.23 Aa	6.5 ±0.3 Cc	13.3 ±0.22 Aa	8.5 ±0.3 Bb	
Lymphocyte(10^9/l)	4.1±2.1 Aa	2.3±0.3 Cc	5.1±3.1 Aa	3.4±0.3 Bb	2.28
	3.6 ±0.16 Aa	1.69±0.25 Cc	4.4 ±0.15 Aa	1.6±0.29 Bb	
Granulocyte(10^9/l)	4.7±0.8 Aa	2.1±1.1 Cc	5.7±0.9 Aa	3.1±1.1 Bb	3.25
	6.1 ±0.5 Aa	5.3 ±0.4 Cc	7.1 ±0.5 Aa	6.2 ±0.3 Bb	
Mid-range absolute count(10^9/l)	1.36 ±0.05 Aa	0.79±0.11 Cc	1.33±0.06 Aa	0.66±0.12 Cc	0.6
	1.1 ±0.04 Aa	1±0.22 Cc	1.32 ±0.05 Aa	1.4±0.22 Bb	

As shown in Table 1, the Values are expressed as mean ± SE, each group containing five animals.

The individual capital letters indicate statistically significant differences between groups within the same line at (P≤0.05).

The individual small letters indicate statistically significant differences between times within one column.

Discussion

The present study investigated the hematological effects of repeated therapeutic doses of ivermectin in rabbits and evaluated the potential protective role of vitamin B12 when co-administered. The findings clearly demonstrate that repeated admin-istration of ivermectin led to significant hematological alterations, including reductions in total white blood cells (WBCs), lymphocytes, red blood cells (RBCs), plate-lets, and mean corpuscular hemoglobin concentration (MCHC), while other parame-ters such as hemoglobin (HGB), packed cell volume (PCV), and plateletcrit (PCT) were not significantly affected.

The observed leukopenia and lymphopenia in the ivermectin-only group are con-sistent with previous studies that reported immunosuppressive or cytotoxic effects of ivermectin on blood cells. The mechanism is likely related to ivermectin's action on ligand-gated chloride channels, particularly GABA and glutamate-gated chloride channels, which can cause increased membrane permeability, ion imbalance, and ultimately apoptosis in non-target mammalian cells (Tribiños *et al*., 2023; Chhaiya *et al*., 2012) [20, 7]. Additionally, the lipophilic nature of ivermectin facilitates its accumu-lation in tissues, potentially disrupting the function of hematopoietic organs such as the liver and bone marrow (Chaccour *et al*., 2017; Arise & Malomo, 2009) [6, 3].

Interestingly, while some studies, such as Abdel-Rahman & Ali (2021) [1], reported ivermectin-induced leukocytosis in sheep, our results demonstrate the opposite ef-fect in rabbits. This difference may reflect species-specific pharmacokinetics, im-mune responses, or methodological differences including dose frequency and obser-vation periods. In acute settings, ivermectin may transiently stimulate the immune system, but chronic exposure, as in this study, appears to result in suppression or de-pletion of immune cells.

The significant decline in RBC count and MCHC indicates that ivermectin may im-pair erythropoiesis, either directly through bone marrow suppression or indirectly through liver toxicity, which can influence erythropoietic regulation. Previous toxi-cological studies in rodents have shown that ivermectin at high or repeated doses can cause hepatocellular degeneration and oxidative stress, both of which are known to impact red blood cell production (GabAllh *et al*., 2017) [8].

In contrast, the co-administration of vitamin B12 with ivermectin showed partial restoration of hematological parameters, particularly in RBCs, HGB, and WBCs. Vitamin

B12 (cobalamin) is essential for DNA synthesis and cellular replication, especially in rapidly dividing cells such as those in the bone marrow. Its role in methylation reactions, maintenance of myelin integrity, and reduction of homocysteine levels makes it crucial for both hematological and neurological health (O'Leary & Samman, 2010) [13]. The beneficial effects observed in this study suggest that B12 may counteract some of the toxic effects of ivermectin by supporting bone marrow function and reducing oxidative damage.

Moreover, vitamin B12 has been shown in various animal studies to enhance im-mune responses and improve hematological profiles under stress or toxic conditions. Its use as a supportive therapy in antiparasitic treatment regimens may, therefore, improve outcomes by maintaining physiological homeostasis and minimizing drug-induced side effects.

Taken together, these findings highlight the negative hematological impact of repeated ivermectin administration in rabbits, while also demonstrating the potential therapeutic benefit of vitamin B12 in mitigating such effects. This suggests that caution should be taken when using ivermectin chronically, particularly in vulnerable populations or species, and that vitamin supplementation may be a valuable adjunct to reduce hepatotoxicity.

Conclusion

This study demonstrates that repeated therapeutic administration of ivermectin in rabbits induces significant hematological disturbances, particularly reductions in white blood cells as well as lymphocytes, red blood cells, and mean corpuscular hemoglobin concentration. These alterations suggest immunosuppressive and erythropoietic impairments potentially linked to ivermectin's pharmacodynamic effects and its influence on hematopoietic tissues. Importantly, co-administration of vitamin B12 provided partial hematological restoration, evidenced by improved red blood cell indices and white blood cell counts. This highlights the protective and supportive role of vitamin B12 in mitigating ivermectin-induced hematotoxicity. The findings advocate for cautious use of ivermectin in prolonged or repeated dosing regimens and suggest that concurrent supplementation with hematopoietic-supportive agents such as vitamin B12 may enhance safety and preserve physiological homeostasis.

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