



SHORT COMMUNICATION

Effects of ivermectin on cytokine and immunoglobulin levels in sheep

Efectos de la ivermectina en los niveles de citoquinas e inmunoglobulinas en ovejas

Efeitos da ivermectina nos níveis de citocinas e imunoglobulinas em ovinos

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Abstract

Background: Ivermectin may affect the levels of cytokines and immunoglobulins in sheep, considering that avermectins have an effect on the immune system. **Objective:** To determine whether ivermectin has an effect on cytokines and immunoglobulins in sheep. **Methods:** After administration of ivermectin to 10 healthy sheep, sheep-specific interferon- α , tumor necrosis factor- α , interleukin-2, interleukin-6, interleukin-10, immunoglobulin G, immunoglobulin M, and immunoglobulin E levels were measured with an ELISA reader. **Results:** Significant ($p < 0.05$) fluctuations were detected in interleukin-2 and interleukin-10 levels. Transient increases ($p < 0.05$) were measured in tumor necrosis factor- α and immunoglobulin E levels ($p < 0.05$). **Conclusion:** Ivermectin may affect immune system parameters in healthy sheep; however, the effects of ivermectin administration on infected sheep should be investigated.

Keywords: avermectins; immunity; immunoglobulin E; immunoglobulin G; immunoglobulin M; interferon- α ; interleukin-2; interleukin-6; interleukin-10; ivermectin; sheep; tumor necrosis factor- α .

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Resumen

Antecedentes: La ivermectina puede alterar los niveles de citocinas e inmunoglobulinas en ovinos, dado que las avermectinas afectan el sistema inmunológico. **Objetivo:** Determinar si la ivermectina tiene algún efecto sobre las citocinas e inmunoglobulinas en ovinos. **Métodos:** Después de la administración de ivermectina a 10 ovejas sanas los niveles de interferón- α específico de oveja, factor de necrosis tumoral- α , interleucina-2, interleucina-6, interleucina-10, inmunoglobulina G, inmunoglobulina M, e inmunoglobulina E se midieron con un lector ELISA. **Resultados:** Se detectaron fluctuaciones significativas ($p < 0,05$) en los niveles de interleucina-2 e interleucina-10. También se encontraron aumentos transitorios ($p < 0,05$) en los niveles de factor de necrosis tumoral- α e inmunoglobulina E ($p < 0,05$). **Conclusión:** la ivermectina puede afectar los parámetros del sistema inmunitario en ovejas sanas.

Palabras clave: avermectinas; factor de necrosis tumoral- α ; inmunoglobulina E; inmunoglobulina G; inmunidad; inmunoglobulina M; interferón- α ; interleucina-2; interleucina-6; interleucina-10; ivermectina; oveja.

Resumo

Antecedentes: A ivermectina pode alterar os níveis de citocinas e imunoglobulinas em ovinos, visto que as avermectinas afetam o sistema imunológico. **Objetivo:** Determinar o efeito da ivermectina nas citocinas e imunoglobulinas em ovinos. **Métodos:** Após a administração de ivermectina a 10 ovelhas saudáveis, interferon- α específico de ovelha, fator de necrose tumoral- α , interleucina-2, interleucina-6 e interleucina-10, os níveis de imunoglobulina G, imunoglobulina M e imunoglobulina E foram medidos com Leitor de ELISA. **Resultados:** Flutuações estatisticamente significativas ($p < 0,05$) foram detectadas nos níveis de interkeukin-2 e interkeukin-10. Aumentos transitórios ($p < 0,05$) foram medidos nos níveis de fator de necrose tumoral- α e imunoglobulina E ($p < 0,05$). **Conclusão:** A ivermectina pode afetar parâmetros do sistema imunológico em ovinos saudáveis, entretanto, os efeitos da administração de ivermectina em ovinos infectados devem ser investigados.

Palavras-chave: avermectinas; fator de necrose tumoral- α ; imunoglobulina E; imunoglobulina G; imunoglobulina M; imunidade; interferão- α ; interleucina-2; interleucina-6; interleucina-10; ivermectina; ovelha.

Introduction

Ivermectin, a macrocyclic lactone, is used orally or parenterally for the treatment of nematodes or ectoparasites in many animal species (Yazar, 2020) and humans (Ashour, 2019). It is used in the therapy of gastrointestinal, eye, and lung nematodes, filariasis and ectoparasites in sheep (Yazar, 2020). It can affect the immune system by affecting cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-6 (Bekdur *et al.*, 2018), and immunoglobulins (Yan *et al.*, 2011). Interleukins can be proinflammatory or anti-inflammatory, depending on the role they play in inflammation. Interferon (IFN)- α , TNF- α , and IL-6 are proinflammatory cytokines, while IL-2 and IL-10 are anti-inflammatory cytokines. Interferons mainly show antiviral activity, TNF- α is an important mediator of acute infection, and IL-6 stimulates the synthesis of acute-phase proteins and immunoglobulins (Akdogan and Yontem, 2018). Five different types of immunoglobulins are secreted by B lymphocytes. IgG is the most abundant immunoglobulin. IgM is synthesized in the acute phase of infections, after which it decreases and is replaced by IgG (Yilmaz and Akgul, 2014). IgE is normally found at very low levels and is associated primarily with allergic reactions (Amarasekera, 2011).

As ivermectin can stimulate the immune system (Blakley and Rousseaux, 1991; Omer *et al.*, 2012), it has been hypothesized that ivermectin administration to healthy sheep might affect specific immune system components such as cytokines and immunoglobulins. The aim of this study was to investigate possible short-term effects of ivermectin on cytokines (IFN- α , TNF- α , IL-2, IL-6, IL-10) and immunoglobulins (IgG, IgM, IgE) in healthy sheep.

Materials and Methods

Ethical considerations

All the procedures were approved by the ethics committee of Selcuk University, Turkey (SUVDAMEK: 2020/79).

Animals and experimental design

Ivermectin (VilmectinTM, Vilsan, Ankara, Turkey) at a dose of 0.2 mg/kg (SC, SID, 3 days) was administered to 10 Anatolian Merino sheep (2.5-3 years old, 61.5-68.5 kg; Ashour, 2019).

Analysis of cytokines and immunoglobulins

ELISA reader (MWGt Lambda Scan 200, Bio-Tec Instruments, Winooski, VT, USA) was used to measure sheep-specific IFN- α (IFN- α Kit, BT Lab, Jiaying, Zhejiang, China), TNF- α (TNF- α Kit, BT Lab), IL-2 (IL-2 Kit, BT Lab), IL-6 (IL-6 Kit, BT Lab) and IL-10 (IL-10 Kit, BT Lab) in sera collected the day before (0 day) and 0.25, 0.5, 1, 2, 3, 4, 5 and 6 days, and IgG (IgG kit, BT Lab), IgM (IgM kit, BT Lab) and IgE (IgE kit, BT Lab) obtained from serum samples taken the day before (0 day) and 1, 3, 7, 10, 13, 16, 19, and 21 days after ivermectin application.

Statistical analysis

Data were evaluated by ANOVA and Duncan's multiple range test (SPSS 22.0). A $p < 0.05$ was considered statistically significant.

Results

Cytokine and immunoglobulin levels are presented in Table 1 and 2, respectively. Significant fluctuations in IL-2 and IL-10, and a temporary increase in TNF- α and IgE levels were observed. However, no statistically significant changes were observed in IFN- α , IL-6, IgG, or IgM levels.

Discussion

In this study, the ivermectin administration protocol followed the common procedure reported in the scientific literature, using 0.2 mg/kg (SID, three days) in the therapy of trichuriasis (Ashour, 2019). Ivermectin caused significant ($p < 0.05$) fluctuations in IL-2 and IL-10 and a temporary increase ($p < 0.05$) in TNF- α , which peaked at day 0.5 (Table 1).

Table 1. The effects of ivermectin (0.2 mg/kg, SC, SID, 3 days) on serum cytokine levels in sheep (mean±SE).

Parameter	0 th day	0.25 th day	0.5 th day	1 st day	2 nd day	3 rd day	4 th day	5 th day	6 th day
INF- α ng/L	50.31±2.93	51.74±3.06	51.81±7.40	50.85±3.47	50.15±3.41	48.77±5.04	42.53±3.67	56.68±2.38	56.42±5.60
TNF- α ng/L	40.12±4.98 ^b	57.12±9.08 ^{ab}	77.04±13.13 ^a	55.56±6.63 ^{ab}	53.87±8.61 ^{ab}	54.28±8.862 ^{ab}	48.93±9.66 ^b	40.96±5.93 ^b	46.52±6.72 ^b
IL-2 ng/L	7.62±2.44 ^{ab}	6.41±2.03 ^{ab}	5.54±1.82 ^{ab}	7.46±2.86 ^{ab}	7.08±3.16 ^{ab}	13.33±3.27 ^a	11.13±2.46 ^{ab}	8.43±2.20 ^{ab}	4.47±1.81 ^b
IL-6 ng/L	9.16±5.97	21.53±10.27	4.88±3.25	14.05±8.98	3.99±3.61	20.25±8.61	8.84±4.58	31.25±13.37	30.59±10.95
IL-10 ng/L	18.84±14.01 ^{ab}	14.45±9.15 ^{ab}	13.08±10.97 ^{ab}	3.81±3.81 ^b	3.42±2.98 ^b	23.99±13.82 ^{ab}	34.20±7.78 ^{ab}	39.77±10.78 ^a	41.86±13.65 ^a

^{a, b}: Different letters in the same line are statistically significant ($p < 0.05$).

Table 2. The effects of ivermectin (0.2 mg/kg, SC, SID, 3 days) on serum immunoglobulins in sheep (mean±SE).

Parameter	0 th day	1 st day	3 rd day	7 th day	10 th day	13 th day	16 th day	19 th day	21 st day
IgG mg/mL	2.25±0.21	2.30±0.15	2.30±0.16	2.49±0.18	2.36±0.29	2.69±0.22	2.34±0.29	2.67±0.32	2.80±0.28
IgM mg/mL	0.28±0.11	0.18±0.09	0.07±0.05	0.19±0.09	0.09±0.06	0.06±0.03	0.14±0.08	0.27±0.12	0.18±0.10
IgE mcg/mL	0.38±0.29 ^b	0.65±0.39 ^b	0.39±0.26 ^b	0.41±0.38 ^b	0.65±0.27 ^b	2.05±0.39 ^a	0.98±0.26 ^b	0.67±0.29 ^b	1.03±0.23 ^b

^{a, b}: Different letters in the same line are statistically significant ($p < 0.05$).

In cattle with papillomatosis, ivermectin administration resulted in a transient non-significant increase in TNF- α and IL-6 levels (Bekdur *et al.*, 2018). In an allergic asthma mouse model, ivermectin induced a decrease in IL-4, IL-5, and IL-13 (Yan *et al.*, 2011). When assessing the effect of ivermectin on cytokines secreted from lipopolysaccharide-induced macrophages *in vitro*, researchers reported that TNF- α and IL-1 β were suppressed, IL-10 was increased, and IL-6 was not affected (Ci *et al.*, 2009). Similarly, after ivermectin was given to mice administered a lethal dose of lipopolysaccharide, it suppressed the production of TNF- α , IL-1 β , and IL-6 (Zhang *et al.*, 2008). In an atopic dermatitis mouse model, ivermectin suppressed the production of several cytokines (Ventre *et al.*, 2017). In the present study, while ivermectin had no significant effect on IgG and IgM levels ($p > 0.05$), it caused a temporary increase in IgE, which peaked on day 13 (Table 2). It also has been shown to reduce IgG and IgE levels and may exert antiallergic effects in an experimental asthma mouse model (Yan *et al.* 2011). In contrast, IgE -found at high levels in patients with hookworm-related cutaneous larva migrans- increased even more after ivermectin administration (Shimogawara *et al.*, 2013). It has been speculated that ivermectin may exert immunostimulatory effects via T lymphocytes (Blakley and Rousseaux, 1991) or macrophages (Omer *et al.*, 2012), possibly providing an alternative approach in immunosuppressed patients. Ivermectin was shown not to be an immunostimulant in healthy dogs (Paradis, 1999) and had no direct effect on the immune response in ectoparasite-infected rabbits and rats (Uhlir and Volf, 1992). These results indicate that the effect of ivermectin on cytokines and immunoglobulins may vary by animal species and disease.

In conclusion, ivermectin at a dose of 0.2 mg/kg (SC, SID, 3 days) to healthy sheep caused changes in several serum cytokines (IL-2, IL-10, TNF- α) and IgE levels. However, these effects of ivermectin may vary according to the disease and animal species.

Declarations

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Conflicts of interest

The authors declare they have no conflicts of interest with regard to the work presented in this report.

Author contributions

Rahmi Canbar, Irmak Dik, Muhittin Uslu, and Enver Yazar wrote and prepared the manuscript. Irmak Dik, Muhittin Uslu, Merve Ider, and Mustafa-Sedat Arslan contributed to the review and approval of the final version of the manuscript. Enver Yazar, Muhittin Uslu, and Irmak Dik worked on the aspects involved in the methodology and statistical analysis. All authors read and agreed with the published version of the manuscript.

References

- Akdogan M, Yontem M. Cytokines. OTSBD; 2018; 3:36–45. <https://doi.org/10.26453/otjhs.350321>
- Amarasekera M. Immunoglobulin E in health and disease. *Asia Pac Allergy* 2011; 1:12–15. <https://doi.org/10.5415/apallergy.2011.1.1.12>
- Ashour DS. Ivermectin: From theory to clinical application. *Int J Antimicrob Ag* 2019; 54:134–142. <https://doi.org/10.1016/j.ijantimicag.2019.05.003>
- Bekdur Y, Aslan O, Senturk M, Cigdem M. The effect of ivermectin on serum TNF- α and IL-6 levels in bovine papillomatosis. *J Health Sci* 2018; 26:156–161. <https://dergipark.org.tr/tr/pub/eujhs/issue/44575/553263>

- Blakley BR, Rousseaux CG. Effect of ivermectin on the immune response in mice (abstract). *Am J Vet Res* 1991; 52:593–595. <https://pubmed.ncbi.nlm.nih.gov/1828942/>
- Ci X, Li H, Yu Q, Zhang X, Yu L, Chen N, Song Y, Deng X. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. *Fundam Clin Pharmacol* 2009; 23:449–455. <https://doi.org/10.1111/j.1472-8206.2009.00684.x>
- Omer MO, Ashra M, Javeed A, Maqbool A. Immunostimulatory effect of ivermectin on macrophage engulfment and delayed type hypersensitivity in broilers. *J Anim Plant Sci* 2012; 22:250–255. www.thejaps.org.pk/docs/v-22-2/01.pdf
- Paradis M. New approaches to the treatment of canine demodicosis. *Vet Clin North Am Small Anim* 1999; 29:1425–1436. [https://doi.org/10.1016/s0195-5616\(99\)50136-8](https://doi.org/10.1016/s0195-5616(99)50136-8)
- Shimogawara R, Hata N, Schuster A, Lesshaft H, De Oliveira SG, Ignatius R, Akao N, Ohta N, Feldmeier H. Hookworm-related cutaneous larva migrans in patients living in an endemic community in Brazil: immunological patterns before and after ivermectin treatment. *Eur J Microbiol Immunol* 2013; 3:258–266. <https://doi.org/10.1556/EuJMI.3.2013.4.4>
- Uhlir J, Volf P. Ivermectin: its effect on the immune system of rabbits and rats infested with ectoparasites. *Vet Immunol Immunopathol* 1992; 34:325–336. [https://doi.org/10.1016/0165-2427\(92\)90173-n](https://doi.org/10.1016/0165-2427(92)90173-n)
- Ventre E, Rozieres A, Lenief V, Albert F, Rossio P, Laoubi L, Dombrowicz D, Staels B, Ulmann L, Julia V, Vial E, Jomard A, Hacini-Rachinel F, Nicolas JF, Vocanson M. Topical ivermectin improves allergic skin inflammation. *Allergy* 2017; 72:1212–1221. <https://doi.org/10.1111/all.13118>
- Yan S, Ci X, Chen N, Chen C, Li X, Chu X, Li J, Deng X. Anti-inflammatory effects of ivermectin in mouse model of allergic asthma. *Inflamm Res* 2011; 60:589–596. <https://doi.org/10.1007/s00011-011-0307-8>
- Yazar E. Chemotherapeutics. In: Yazar E, editor. *Veterinary Drug Guide and Treatment Handbook*. Istanbul: Nobel Tip Publisher; 2020. p.81–233.
- Yilmaz N, Akgul Y. Immunoglobulins and septicemia. *Uludag Univ J Fac Vet Med* 2014; 33:33–42. <https://dergipark.org.tr/tr/download/article-file/412339>
- Zhang X, Song Y, Ci X, An N, Ju Y, Li H, Wang X, Han C, Cui J, Deng X. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. *Inflamm Res* 2008; 57:524–529. <https://doi.org/10.1007/s00011-008-8007-8>