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## **An Overview of Levamisole Hydrochloride with Immuno-Stimulant Activity**

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### **ABSTRACT**

Levamisole, marketed as the hydrochloride salt under the trade name Ergamisol (R12564), is an anti helminthic and immunomodulator belonging to a class of synthetic imidazo-thiazole derivatives. It was discovered in 1966 at Belgium's Janssen pharmaceuticals, where it was prepared initially in the form of its racemate called tetramisole. The two stereoisomers of tetramisole were subsequently synthesized, and the levorotatory isomer was given the name levamisole. Levamisole has been used in humans to treat parasitic worm infections, and has been studied in combination with other forms of chemotherapy for colon cancer, melanoma, and head and neck cancer. In some of the leukemic cell line studies, both levamisole and tetramisole showed similar effect. Effective studies need to be undertaken to study the full potential of levamisole in Immunostimulation activities and immuno synergistic effect of Levamisole with combination to natural polysaccharides.

**Keywords**-Levamisole, Immunostimulation, polysaccharide, Tetramisole

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## INTRODUCTION

Levamisole, an anthelmintic agent with a wide range of immunomodulatory actions, has been used successfully as monotherapy and an adjunct to treatment in a variety of diseases. Levamisole is a promising agent for use in the immunotherapy of patients with deficient host defense mechanisms. Both in anergic patients and in experimental animals levamisole has been shown to stimulate cell mediated immunity probably through the enhanced maturation of cells. Because of its immunomodulating effects Levamisole has been used in a wide range of diseases with and without success. In dermatologic disease Levamisole has been successfully used in the treatment of parasitic, viral and bacterial infections including leprosy, collagen vascular diseases, inflammatory skin diseases and children with impaired immune a variety of reasons. It has also been used in combination with polymers for treating a number of dermatologic disorders, e.g. in combination with cimetidine for treating recalcitrant warts, with prednisolone for treating lichen planus, erythema multiforme and aphthous ulcers of the mouth. Adverse affects of levamisole are mild and infrequent and include rash, nausea, abdominal cramps, taste alteration, alopecia, arthralgia, and a flu-like syndrome. It can rarely cause agranulocytosis <sup>1-5</sup>

### Drug Profile

#### Levamisole:

The levorotatory isomer of tetramisole

#### Synonym:

Levamisol, L-Tetramisole; dl-Tetramisol, Phenyl imidothiazole, Levamisolum, Levamisole hydrochloride<sup>2</sup>.

#### Drug Category:

Adjuvants, Immunologic, Antinematodal Agents, Anti-rheumatic Agents

**Dose:** A single dose of 2.5 mg/kg has been recommended for antihelminthic therapy in humans and a dose of 50 mg, three times a day <sup>3</sup>.

#### Proprietary Names:

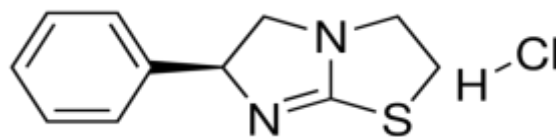
Ergamisole, Nemicide, solaskil, Stimamizol, Tramisole, Worm-chek, Decaris –Vet, Nilverm, Ripercol, Narpenol, Levasole <sup>4</sup>

## CHEMISTRY

#### Chemical Name:

(-)-2, 3, 5, 6-Tetrahydro-6-phenylimidazo-[2, 1-b] thiazole monohydrochloride

**Molecular formulae:** C<sub>11</sub>H<sub>13</sub>ClN<sub>2</sub>S

**Chemical Structure:****Figure1- Structure of Levamisole Hydrochloride <sup>3</sup>****Molecular weight <sup>1</sup>:** 240.7**PHYSICOCHEMICAL PROPERTIES**Description: A white crystalline stable powder <sup>6</sup>.

Taste: Metallic

Odour: Characteristic odour <sup>7</sup>.

Melting Point: 227°C to 229°C.

Solubility: Soluble in water, methanol, slightly soluble in ethanol, very slightly soluble in chloroform, insoluble in acetone <sup>7,8</sup>Optical Rotation:  $[\alpha]_D^{20} = -124 \pm 2^\circ$  (c=0.9 in water)

PH: Levamisole solution has a pH of 3–4.5

UV maxima <sup>7</sup>: 213 nmHeavy metals: maximum 20 ppm. 12 ml of solution S complies with limit test A. Prepare the standard using *lead standard solution (1 ppm Pb) R* <sup>8</sup>.Loss on drying: maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 100-105 °C for 4 h <sup>7</sup>.

Sulphated ash: maximum 0.1 per cent, determined on 1.0 g.

Dissociation Constant: pKa 8

Partition Coefficient: Log P (octanol/water) = 0.64

Storage: Levamisole to be stored in well-closed, light resistant container <sup>10</sup>**PHARMACOLOGY**

Levamisole acts as an anti parasitic, Immunomodulators and adjuvant in colorectal cancer. It appears to restore depressed immune function through stimulating antibody formation and enhance T-cell response by stimulating T-cell activation and proliferation. Anti parasitic action appears to be tied to its agonistic activity towards nicotinic receptors in nematode muscles resulting in spastic paralysis. The net effect is a paralyzing of the worm, which is then expelled live <sup>6-10</sup>.

**Mechanism of action**

The mechanism of action of levamisole as an antiparasitic agent appears to be tied to its agonistic activity towards the L-subtype nicotinic acetylcholine receptors in nematode muscles. This agonistic action reduces the capacity of the males to control their reproductive muscles and limits their ability to copulate. The mechanism of action of Levamisol as an anticancer drug in combination with fluorouracil is unknown. The effects of levamisole on the immune system are complex. The drug appears to restore depressed immune function rather than to stimulate response to above-normal levels. Levamisol can stimulate formation of antibodies to various antigens, enhance T-cell responses by stimulating T-cell activation and proliferation, potentiate monocyte and macrophage functions including phagocytosis and chemotaxis, and increase neutrophil mobility, adherence, and chemotaxis <sup>8-12</sup>

### Indications and usage

- Levamisole is an antihelminthic drug approved for use in human medicine as well as veterinary medicine
- It used as an immunomodulator in rheumatoid arthritis and colorectal cancer therapy.
- A single dose of 2.5 mg/kg has been recommended for antihelminthic therapy in humans and a dose of 50 mg, three times a day, for three days every other week for colon cancer therapy
- Levamisole is used for adjuvant treatment in combination with fluorouracil after surgical rejection in patients with Dukes' stage C colon cancer.
- Levamisole Also used to treat malignant melanoma and head/neck cancer <sup>13</sup>.

### Adverse drug reactions

Significant adverse reactions of levamisole are agranulocytosis, skin rash, and febrile illness, rheumatoid arthritis, blood dyscrasia. Nausea, vomiting, diarrhea, mouth sores, loss of appetite, stomach pain, change in taste and smell, muscle aches, fatigue, dizziness & headache <sup>(5, 11)</sup>.

### Drug interactions

- Anticoagulant effect increases when levamisole combines with Anisindione, Dicumarol, Acenocoumarol, Warfarin <sup>12</sup>
- levamisole hydrochloridenhas been reported to produce "ANTABUSE"-like side effects when given concomitantly with alcohol <sup>12</sup>.
- Concomitant administration of phenytoin and Levamisole fluorouracil has lead to increased plasma levels of phenytoin. The physician is advised to monitor plasma levels of phenytoin and to decrease the dose if necessary.
- By taking levamisole and warfarin sodium, prolongation of the prothrombin time beyond the

therapeutic range found in patients, it is suggested that the prothrombin time should be monitored carefully, and the dose of warfarin sodium or other coumarin-like drugs should be adjusted accordingly, in patients taking both drugs <sup>13</sup>.

### Pharmacokinetics

Levamisole is rapidly absorbed from the GI tract and extensively metabolized in the liver and excreted mainly by the kidneys (70% over 3 days). Its plasma elimination half-life is 4.4-5.6 hours. Due to short elimination half-life, blood levels of levamisole fall more rapidly and go unnoticed in toxicological examination. Data from few clinical studies indicate that the consumption of 50-200 mg/day of levamisole causes agranulocytosis in 0.08 – 5% of the studied population (WHO, FAS 33)<sup>11-13</sup>.

**Table 1-Pharmacokinetics parameters of Levamisole at daily dose**

Sl. No.	Pharmacokinetic Parameters	Value
1	Absorption.	Rapidly absorbed from gastrointestinal tract
2	Fraction Bioavailable (%)	47– 74.2%
3	Elimination half-life (h)	4.4 – 5.6
4	Volume of distribution (lit/Kg)	2-6
5	Protein Binding (%)	20-25%
6	Clearance (lit/min)	0.19 – 0.26
7	C <sub>max</sub> (ng/ml)	82 – 100
8	T <sub>max</sub> (hr)	3
9	Steady state plasma concentration (mg/lit)	1

### Metabolism & Excretion

A single oral labeled levamisole dose in humans was eliminated in urine (60%) and feces (4%) within 24 hours. Urinary products included unchanged drug (3.2%) and free (1.6%) and conjugated (11%) p-OH-levamisole. Aminorex has been identified as a minor urinary metabolite in the horse; reported urine concentrations of levamisole and aminorex following oral or subcutaneous levamisole administration ranged from 210–2754 or 20–330 µg/L, respectively<sup>12-16</sup>.

### Reported Immunostimulant Activities

SOPPI et al. have studied the in vivo effect of levamisole on the PHA and responses of chicken peripheral blood lymphocytes and on the in vivo antibody response to a thymus dependent antigen (BSA) and to a thymus independent antigen (*Brucella abortus*). Levamisole (0-25 mg/kg) increased significantly both the PHA and Con A responses of chicken blood lymphocytes. The antigens were given at the time of enhanced mitogenic responses and a significant increase was observed in both IgM and IgG antibodies to BSA. In contrast, no effect was obtained on antibody

responses to *Brucella abortus* organisms. The results show that levamisole is able to enhance both humoral and cellular immune responses in normal chickens. The effect is probably mediated by the activation of the T cell function and effects only antibody responses to thymus dependent antigen. These findings confirm and extend the observations regarding the ability of levamisole to modulate immune responses<sup>17</sup>.

Wang et al. have explored the effects of liniment levamisole on cellular immune functions of patients with chronic hepatitis B. The levels of T lymphocyte subsets and mIL-2R in peripheral blood mononuclear cells (PBMCs) were measured by biotin-streptavidin (BSA) technique in patients with chronic hepatitis B before and after the treatment with liniment levamisole. After one course of treatment with liniment levamisole, the levels of CD3+, CD4+, and the ratio of CD4+/CD8+ increased as compared to those before the treatment but the level of CD8+ decreased. The total expression level of mIL-2R in PBMCs increased before and after the treatment with liniment levamisole. Liniment levamisole may reinforce cellular immune functions of patients with chronic hepatitis B<sup>18</sup>.

Jaya et al. have determined the immunomodulatory effect of dietary levamisole in Asian catfish (*Clarias batrachus*), fish were fed four different diets for 10 days: a formulated diet as control and the same diet supplemented with 50, 150 or 450 mg levamisole kg<sup>-1</sup> feed. The serum bacterial agglutination titre against *Aeromonas hydrophila* as a measure of specific immunity, serum haemagglutination titre, natural haemolytic complement activity (ACH50), myeloperoxidase and lysozyme activities, total protein level and oxidative radical production by neutrophils as a measure of non-specific immunity as well as disease resistance against a *hydrophila* challenge to separate vaccinated and non-vaccinated groups were evaluated at 0, 1, 2 and 3 weeks after last administration of levamisole. Levamisole supplement at the lowest level (50 mg kg<sup>-1</sup>) significantly enhanced oxidative radical production and serum myeloperoxidase (MPO) content immediately after 10 days of feeding, which reached peak values after 3 and 2 weeks of feeding respectively. Haemolytic complement and haemagglutination titre were significantly enhanced after 3 and 1 weeks respectively<sup>19</sup>.

Tekade et al. have studied in birds treated with Cyclophosphamide @ 150 mg/kg body weight I/V on 21st day of age produced marked immunosuppression. Administration of *A. racemosus*, *Sida cordifolia* in combination with Levamisole was the more effective in producing immunomodulatory effect in immunosuppressed birds<sup>20</sup>

Sajid et al. have determined the immunomodulatory effect of dietary intake of levamisole in the common carp, specimen were fed diets containing 0 (control), 125, 250 and 500 mg levamisole

kg-1 of dry diet for a period of 70 days. Experimental stock was challenged intra-peritoneally with *Aeromonas hydrophila* on 30th and 58th day. Hematobiochemical parameters were determined on day 0, 57 and day 70. The total erythrocyte count, haemoglobin content, hematocrit value, total serum protein, albumin and globulin content were significantly ( $P<0.05$ ) enhanced in levamisole supplemented groups particularly in 250 mg kg-1 group; however the TLC was significantly ( $P<0.05$ ) higher in control (infected) group. Lysozyme activity and NBT assay were significantly stimulated in levamisole supplemented groups displaying the highest value in 250 mg kg-1 group on day 57<sup>21</sup>.

### Discussion

Levamisole exert its immunopotentiating activity in patients with chronic diseases. As an immune stimulant, levamisole connected with receptors of thymopentin on the surfaces of immunologic cells and induces inhibited T lymphocytes into immunologically competent cells. According to clinical experiments, levamisole has therapeutic effectiveness and boosts immunity in a variety of infectious diseases and some cancers. This review helps in further research to search for a new immunosynergistic molecule by taking levamisole as a model immunostimulating drug.

### REFERENCES

1. Indian Herbal Pharmacopoeia Revised New Edition. Published by Indian Drug Manufacturer's Association, Mumbai; 2002: 429-438.
2. Nadkarni KM. Indian Meteria Medica, Published by Ramdas Bhatkal for Popular Prakashan Pvt.Ltd.Mumbai; 2002: 202-205.
3. Vaidyaratnam PS. Varier's. Indian Medicinal Plants, Published by Orient Longman Private Ltd. Chennai; 2004: 258-262.
4. The Ayurvedic Pharmacopoeia of India, first edition. Published by The controller of Publications. Civil Lines, New Delhi; 2001: 252.
5. A. H. M. Raeymakers. Biological response modifier with anthelmintic activity. J. Med. Pharm. Chem; 1966: 545-551.
6. Sadigh-Eteghad S, khayat-Nuri, H Abadi N, Ghavami S, Golabi M, Shanebandi D. Synergetic effects of oral administration of levamisole and Echinacea purpurea on immune response in Wistar rat. Res Vet Sci 2011; 91: 82–85.
7. Vandamme TF, Demoustier, M Rollmann B. Quantitation of levamisole in plasma using high performance liquid chromatography. Eur. J. Drug Metab. Pharmacokinet 1995; 20:

- 145-149.
8. Koyma K, Oshi T, Ishii A, Deguchi T. Levamisole: Metabolic fate of levamisole in rats, dogs and monkey. *oyo yakuri* 1983; 26: 869-876.
  9. JG Adams. Pharmacokinetics of Levamisole. *J. Rheum* 1978; 5: 137–142.
  10. SA. Barker. The formation of aminorex in racehorses following levamisole administration. A quantitative and chiral analysis following synthetic aminorex or levamisole administration vs. aminorex-positive samples from the field: a preliminary report. *J. Vet. Pharm & Ther* 2008; 32: 160–166.
  11. M Bradford, B Rosenberg, J Moreno, G Dumyati. Bilateral necrosis of earlobes and cheeks: another complication of cocaine contaminated with Levamisole. *Ann. Int. Med* 2010; 152: 758–759.
  12. Mutch RS, Hutson PR. Levamisole in the adjuvant treatment of colon cancer. *Clin Pharm* 1991; 10: 95-109.
  13. Stevenson HC. Levamisole: Known effects on the immune system, clinical results and future applications in the treatment of cancer. *J Clin Oncol* 1991; 9: 2052-66.
  14. JM Reid, JS Kovach, MJ O Connell. Clinical and pharmacokinetic studies of high-dose levamisole in combination with 5-fluorouracil in patients with advanced cancer. *Canc. Chemothera Pharm* 1998; 41: 477–484.
  15. F Rousseau, JM Haquenoer, D Lesieu, AP Gamot. Gas-chromatographic determination of levamisole in human plasma-normalization and reliability of the method. *Eur. J. Drug Metab. Pharmacokin* 1981; 6: 281–288.
  16. P Sari, J Sun, M Razzak, IG. Tucker. HPLC assay of levamisole and abamectin in sheep plasma for application to pharmacokinetic studies. *J. Liq. Chrom Rel. Tech* 2006; 29: 2277–2290.
  17. E. Soppi, O Lassila, M K Viljanen, OP Lehtonen, J Eskola. In-vivo effect of levamisole, on cellular and humoral immunity in normal chickens. *Clin.exp. Immunol* 1979; 38: 609- 614.
  18. Ke Xia Wang , Li Hua Zhang , Jiang Long Peng , Yong Liang , Xue Feng Wang , Hui Zhi , Xiang Xia Wang, Huan Xiong Geng. Effect of liniment levamisole on cellular immune functions of patients with chronic hepatitis B. *World J Gastroenterol* 2005; 11: 7208-7210.
  19. Jaya Kumari, Pramoda K Sahoo. Dietary levamisole modulates the immune response and disease resistance of Asian catfish *Clarias batrachus* (Linnaeus). *Aquaculture Research* 2006; 37: 500-509.

20. Tekade S H, S G Mode, S P Waghmare. Effect of *Asparagus racemosus*, *Sida cordifolia* and levamisole on immunological parameters in experimentally induced immunosuppressed broilers. Veterinary World 2008; 1: 49-50.
21. Sajid Maqsood, MH Samoon, Prabjeet Singh. Immunomodulatory and Growth Promoting Effect of Dietary Levamisole in *Cyprinus carpio* Fingerlings against the Challenge of *Aeromonas hydrophila*. Tur J of Fis and Aq Sc 2009; 9: 111-120.



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