CHAPTER 22

LEVAMISOLE USES IN DERMATOLOGY

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INTRODUCTION

Levamisole is a synthetic imidazothiazole derivative that has been widely used in the treatment of worm infestations in both humans and domestic animals as an anthelmintic drug. Levamisole is a broad spectrum anthelmintic agent, which is primarily used for expelling Ascaris and hook worms. Levamisole is the levoisomer of tetramizole, a heterocyclic aromatic amine. Compared with tetramizole, it has the advantage of fewer side effects, higher curative effects, and smaller dosage required for clinical treatment.[1,2]

The racemic form of levamisole, tetramisole, was first disclosed as an anthelmintic agent in the 1960s by Janssen Pharmaceutica. Levamisole was introduced as a broad spectrum veterinary anthelmintic in 1965 and an anthelmintic in humans in 1966.[3] It has found wide application in the treatment of worm infestations and eliminating intestinal parasites in both humans and animals.[2]

In the 1990s, several reviews about levamisole's efficacy as a human immune system modulator appeared in the literature, which focused on its potential beneficial effects in cancer treatment. Results were mixed with some trials showing enhanced chemotherapeutic activity.[4]

In 1991, the racemic form of levamisole hydrochloride (marketed under the trade name of Ergamisol) was approved by the U.S. Food and Drug Administration foruse as adjuvant therapy with fluorouracil in the treatment of colorectal cancer. "However, the drug was voluntarily removed from the U.S. market in 2000 because of the common occurrence of agranulocytosis".[5] However, it persists as a public health issue because of its use as a bulking agent in distributed cocaine.[6] Because of this, levamisole is being detected in increasing percentages of cocaine in the United States and worldwide.[7,8]

Levamisole was recognized as a cocaine adulterant in the United States in 2002. Since then, the percentage of cocaine contaminated by levamisole in Europe and the United States rose steadily to reach approximately 69% in 2009.[6] However, it remains available in veterinary medicine in many countries such as the United States, Canada, Italy, and South America.[9]

Pharmacokinetics

Levamisole, or (S)-6-phenyl-2,3,5,6-tetrahydroimidazo [2,1-b]-[1,3] thiazole, is a synthetic imidazothiazole derivative that has been administered to humans as an anthelmintic and immunomodulator agent since 1966; the molecular formula is C11H12N2S, and the molecular weight is 204.286 g/mol. The drug, marketed with several trade names (Decazole, Ergamisol, Levasole, Tramisole, and Vermisole), is also available as ahydrochloride or phosphate salt, in powder or tablet form; it is used as a veterinary anthelmintic by oral administration, or in solutions for subcutaneous injection. Levamisole has been employed to treat cattle, sheep, poultry, and pigs against stomach, intestinal, and lung worms.[10]

No liquid dosage form of levamisole is available. An oral solution would be highly desirable for children who are unable to swallow tablets and allows the dose to be easily adjusted.[11]

In humans, levamisole is rapidly absorbed after oral administration at a dose of 150 mg, with an approximate oral bioavailability of 62.5%.[12]

Levamisole is rapidly absorbed from the gastrointestinal tract and intramuscular or subcutaneous injection sites and is very well distributed in all tissues.[13] Peak blood levels are obtained after 1.5–4 hours. The plasma elimination half-life of levamisole is estimated to be 5.6 hours in humans. Human mass balance studies with orally administered levamisole (150 mg) indicate metabolism as a predominant route of elimination.[14] Levamisole is extensively metabolized in the liver and its metabolites have a half-life of 16 hours. The drug is excreted primarily in urine as metabolites. Approximately 70% of an administered dose is excreted in the urine over threedays. The rest is excreted as metabolites in the feces or unchanged in the urine.[12,15,16] Only approximately 3.2% of the oral dose was recovered as unchanged drug in the urine.[12,16]

If needed, levamisole can be detected in urine and plasma by gas chromatography mass spectroscopy at local public health departments, reference laboratories, and crimelaboratories. Because the plasma half-life of levamisole is relatively short (estimated population

Atopic diseases

Kocabas et al.[92] found that the use of levamisole may have important implications in the management of the allergic inflammation. Levamisole suppresses the Th2 immune response and elicits the Th1 response via inducing more secretion of INF-γ from T cells. As an immune-enhancing agent, it was attempted in the treatment of atopic disease, leprosy, and cancer.[93]

Chronic idiopathic urticaria

Zhang et al.[94] indicated that a combination of levamisole with levocetirizine is more effective than levocetirizine alone for the treatment of chronic idiopathic urticaria.

Angiolymphoid hyperplasia with eosinophilia

Levamisole has been found to be effective in the treatment of the disseminated form of angiolymphoid hyperplasia with eosinophilia, whose etiology is still unknown.[95]

Kimura's disease

Yu et al.[96] reported the case of a 6-year-old boy with Kimura's disease and concurrent steroid dependent minimal change nephrotic syndrome. With levamisole treatment for 24 months, tumor progression and relapse of the associated nephrotic syndrome were not observed.

Melanoma

Lynn et al.[97] conducted a randomized double-blind trial of levamisole versus placebo as adjuvant therapy for the surgical treatment of melanoma. Of 203 patients included in the study, 104 received levamisole and 99 received a placebo. This study concluded that levamisole had no benefit, as compared to the placebo, as adjuvant therapy for malignant melanoma. Unfortunately, the promise of prolonged survival from metastatic melanoma in earlier studies with levamisole not realized.[47,98,99]

Burns

Levamisole has been used successfully to treat depressed immune function and susceptibility to infections after burn injuries in several animal models. Although no controlled trials are available, some benefit has also been noted in patients with burn injuries.[100]

REFERENCES

1. Noah S, Joshua DR, Jeffrey MW. Levamisole in dermatology: a review. Am J Clin Dermatol 2004; 5: 97–104.
2. Kamal A, Khanna GB, Krishnaji T, Ramu R. A new facile chemoenzymatic synthesis of levamisole. Bioorg Med Chem Lett 2005; 15: 613–5.
3. Janssen PA. The levamisole story. Prog Drug Res 1976; 20: 347–83.
4. Greenspan EM, Erlich R. Levamisole and the newer of chemoimmunotherapy. Cancer Invest 1991; 9: 111–24.
5. Ullrich K, Koval R, Koval E, Bapoje S, Hirsh JM. Five consecutive cases of a cutaneous vasculopathy in users of levamisole-adulterated cocaine. J Clin Rheumatol 2011;17: 193–6.
6. Lee KC, Ladizinski B, Federman DG. Complications associated with use of levamisole contaminated cocaine: an emerging public health challenge. Mayo Clin Proc 2012;87(6):581-6.
7. Pearson T, Bremmer M, Cohen J, Driscoll M. Vasculopathy related to cocaine adulterated with levamisole: a review of the literature. Dermatol Online J 2012;18(7):1.
8. Chang A, Osterloh J, Thomas J. Levamisole: a dangerous new cocaine adulterant. Clin Pharmacol Ther 2010;88: 408–11.
9. Czuchlewski DR, Brackney M, Ewers C, Manna J. Clinicopathologic features of agranulocytosis in the setting of levamisole-tainted cocaine. Am J Clin Pathol 2010;133:466–72.
10. JECFA, Joint FAO/WHO Expert Committee on Food Additives. Levamisole. WHO Food Additive Series 1991; 27: 75–101.
11. Chiadmi F, Lyer A, Cisternino S et al. Stability Of Levamisole Oral Solutions Prepared From Tablets And Powder. J Pharm Pharmaceut Sci 2005;8(2):322-5.
12. Kouassi E, Caille G, Le´ry L, Lariviere , Vezina M. Novel assay and pharmacokinetics of levamisole and p-hydroxy levamisole in human plasma and urine. Biopharm Drug Dispos 1986; 7: 71–89.
13. Renoux G. Modulation of immunity by levamisole. J Pharmacol Ther 1978; 2: 288-96.
14. Adams JG. Pharmacokinetics of levamisole. J Rheumatol Supp 1978;l4:137–42.
15. Sweetman SC. Martindale: the complete drug reference. 33rd ed. Chicago (IL): Pharmaceutical Press 2002:1253-4.
16. Reid JM, Kovach JS, O'Connell MJ, Bagniewski PG, Moertel CG. Clinical and pharmacokinetic studies of high-dose levamisole in combination with 5-fluoroacil in patients with advanced cancer. Cancer Chemother Pharmacol 1998;41: 477–84.
17. Buchanan JA, Heard K, Burbach C et al. Prevalence of levamisole in urine toxicology screens positive for cocaine in an inner-cityhospital. JAMA 2011;305:1657–8.
18. Lynch KL, Dominy SS, Graf J et al. Detection of levamisole exposure in cocaine users by liquid chromatography-tandem mass spectrometry. J Anal Toxicol 2011;35: 176–8.
19. Gennaro AR. Remington: the science and practice of pharmacy. 19th ed. Easton (PA): Mack Publishing Co. 1995:101-2.
20. Holcombe RF, McLaren CE, Milovanovic T. Immunomodulation with low dose levamisole in patients with colonic polyps. Cancer Detect Prev 2006;30(1):94–8.
21. Sanchez MR. Miscellaneous Treatments: Thalidomide, Potassium Iodide, Levamisole, Clofazimine, Colchicine, and D-Penicillamine. Clin Dermatol 2000;18: 131–45.
22. Ohguro Y, Imamura T, Hara T et al. Study on safety of KW-2-LE-T (Levamisole HCI). Reproductive studies. Yakuri to Chiryo 1982;10: 3155–67.
23. Kurishita A. Suppressive effects of two bioresponse modifiers, krestin and levamisole, on 5-azaclytidine-induced digital defects in rats. Teratog Carcinog Mutagen 1990; 10: 409–15.
24. Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. 5th ed. Baltimore: Williams and Wilkins; 1998.

25. Czeizel AE, Rockenbauer M, Siffel Cs, Varga E. Description and mission evaluation of the Hungarian Case-Control Surveillance of Congenital Abnormalities, 1980–1996. Teratology 2001; 63: 176–85.
26. Robertson SJ, Martin RJ. Levamisole-activated single-channel currents frommuscle of the nematode parasite Ascaris suum. Br J Pharmacol 1993;108:170–8.
27. Kaplan RM. Drug resistance in nematodes of veterinary importance: a status report. Trends Parasitol 2004; 20:477–81.
28. Schiller H, Lindstrom M, Patricia L et al. Immunological Effects of Levamisole In Vitro Joan Borden Journal of Immunolherapy Raven Press, Ltd., New York 1991;10:297-306.
29. Goldstein G. Mode of action of levamisole. J Rheumatol Suppl 1978;4: 143-8.
30. Buchanan JA, Lavonas EJ. Agranulocytosis and other consequences due to use of illicit cocaine contaminated with levamisole. Curr Opin Hematol 2012;19(1):27-31.
31. Holcombe RF, Stewart RM. Augmentation of IL12-dependent Th1 cytokine production by levamisole. Allergy Clin Immunol Int 1997;9: 119–20.
32. Friis T, Engel AM, Klein BM, Rygaard J, Houen G. Levamisole inhibits angiogenesis in vitro and tumor growth in vivo. Angiogenesis 2005; 8: 25-34.
33. Cheng YC, Po HL. Leukoencephalopathy after Levamisole for the Treatment of Verrucae. Acta Neurol Taiwan 2011; 20: 262-6.
34. Kaplan B, Cardarell C, Pinnell SR. Levamisole and agranulocytosis. Cutis 1979; 24: 429-30.
35. Rongioletti F, Ghio L, Ginevri F et al. Purpura of the ears: a distinctive vasculopathy with circulating autoantibodies complicating long-term treatment with levamisole in children. Br J Dermatol 1999;140:948-51.
36. Gaertner EM, Switlyk SA. Dermatologic complications from levamisole-contaminated cocaine: a case report and review of the literature. Cutis 2014;93(2):102-6.
37. Symoens J, Veys E, Mielants M et al. Adverse reactions to levamisole. Cancer Treat Rep 1978; 62: 1721-30.
38. Gupta R, Gupta S. Fever due to levamisole. Indian J Dermatol Venereol Leprol 2003;69(3):237-8.
39. Secher L, Permin R, Skov PS et al. Levamisole induced hypersensitivity. Acta Derm Venereol 1978; 58: 372-4.
40. Gross RL, Brucker J, Bahce-Aluntas A et al. A novel cutaneous vasculitis syndrome induced by levamisole-contaminated cocaine. Clin Rheumatol 2011;30: 1385–92.
41. Mouzakis J, Somboonwit C, Lakshmi S et al. Levamisole induced necrosis of the skin and neutropenia following intranasal cocaine use: a newly recognized syndrome. J Drugs Dermatol 2011;10(10):1204-07.
42. Pasricha JS, Khera V. Effect of prolonged treatment with levamisole on vitiligo with limited and slow-spreading disease. Int J Dermatol 1994;33: 584-7.
43. Scheinfeld N, Rosenberg JD, Weinberg JM. Levamisole in dermatology: review article. Am J Clin Dermatol 2004; 5: 97–104.
44. Printzis S, Raptopoulou-Gigi M, Orphanou-Koumerkeridou H et al. Immunotherapy in chronic brucellosis. Effect of levamisole and interferon; mechanisms of action and clinical value. Immunopharmacol Immunotoxicol 1994; 16: 679–93.
45. Ruiz-Moreno M, García R, Rua MJ et al. Levamisole and interferon in children with chronic hepatitis B. Hepatology 1993;18(2):264–9.
46. Janik J, Kopp WC, Smith JW et al. Dose-related immunologic effects of levamisole in patients with cancer. J Clin Oncol 1993; 11: 125–35.
47. Quirt IC, Shelley WE, Pater JL et al. Improved survival in patients with poor-prognosis malignant melanoma treated with adjuvant levamisole: A phase III study by the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1991; 9: 729 –35.
48. Moertel CG, Fleming TR, MacDonald JS et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med 1995;122(5):321-6.
49. Papageorgiou P, Kesarwala HH, Alcid DV et al. Levamisole in chronic pyoderma. J Clin Lab Immunol 1982; 8: 121-7.
50. Djawari D, Hornstein OP. Recurrent chronic pyoderma with cellular immunodeficiency: successful therapy by levamisole. Dermatologica 1980;161:116-23.
51. Svejgaard E, Christiansen AH, Stahl D et al. Clinical and immunological studies in chronic dermatophytosis caused by Trichophyton rubrum. Acta Derm Venereol 1984; 64: 493-500.
52. Medvedev IuA, Alekhin EK, Leshchenko VM. Use of immunostimulants in the treatment of a zooanthroponotic trichophyton infection. Vestn Dermatol Venerol 1987; 11: 70-3.
53. Paul Y, Singh J. Cutaneous larva migrans in an infant. Indian Pediatr 1994; 31: 1089-91.
54. Parsad D, Pandhi R, Juneja A et al. Cimetidine and levamisole versus cimetidine alone for recalcitrant warts in children. Pediatr Dermatol 2001; 18: 349-52.
55. Parsad D, Saini R, Negi KS. Comparison of combination of cimetidine and levamisole with cimetidine alone in the treatment of recalcitrant warts. Australas J Dermatol 1999; 40: 93-5.
56. Amer M, Tosson Z, Soliman A, Selim AG, Gendy AA. Verrucae treated by levamisole. Int J Dermatol 1991; 30: 738-40.
57. Saul A, Sanz R, Gomez M. Treatment of multiple viral warts with levamisole. Int J Dermatol 1980; 19: 342-3.
58. Seidlin M, Straus SE. Treatment of mucocutaneous herpes simplex infection. Clin Dermatol 1984; 2: 100-16.
59. Constantopoulos A, Lagos P, Benetos S et al. Disseminated neonatal herpes simplex infection treated with levamisole: report of a case. Dermatologica 1980;160:121-4.
60. Hernandez-Perez E. Levamisole plus Indomethacin in the Treatment of Herpes simlex. Dermatologica 1980:160;118-20.
61. Tanphaichitra D, Srimuang S. Efficacy of acyclovir combined with immunopotentiating agents in the treatment of varicella-zoster. J Antimicrob Chemother 1987;19:255-62.
62. Lai WH, Lu SY, Eng HL. Levamisole Aids in Treatment of Refractory Oral Candidiasis in Two Patients with Thymoma Associated with Myasthenia Gravis: Report of Two Cases. Chang Gung Med J 2002;25(9):606-11.
63. Kaya EG, Ozbilge H, Ustundag MB, Torun YA. The effects on immune response of levamisole treatment following infection of U-937 macrophages with Candida albicans. Acta Microbiol Immunol Hung 2011;58(4):279-88.
64. Namazi MR. Levamisole: a safe and economical weapon against pediculosis. Int J Dermatol 2001; 40: 292-4.
65. Butler PG. Levamisole and immune response phenomena in cutaneous leishmaniasis. J Am Acad Dermatol 1982;6(6):1070-7.
66. Martinez D, Zaias N. Levamisole as adjunct to dapsone in leprosy. Lancet 1976;II:209-10.
67. Bera DK, Sen PC. Effect of Levamisole on Bacterial Index inBL and LL Leprosy. Int J Lepr Other Mycobact Dis 1985;53(2):198-200.

68. Lu SY, Chen WJ, Eng HL. Response to levamisole and low dose prednisolone in 41 patients with chronic oral ulcers. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998; 86: 438–45.
69. Glick M, Muzyka BC. Alternative therapies for major aphthous ulcers in AIDS patients. J Am Dent Assoc 1992; 123: 61-5.
70. Elsen D, Lynch DP. Selecting topical and systemic agents for recurrent aphthous stomatitis. Cutis 2001; 68: 201–6.
71. Sharda N, Shashikanth MC, Kant P, Jain M. Levamisole and low-dose prednisolone in the treatment of recurent aphthous stomatitis J Oral Pathol Med 2014;43(4):309–16.
72. Sun A, Chiang CP, Chiou PS et al. Immunomodulation by levamisole in patients with recurrent aphthous ulcers or oral lichen planus. J Oral Pathol Med 1994;23: 172–7.
73. Dash R, Panda R, Mishra SS, Das PC, Mishra KC. Levamisole in recurrent aphthous stomatitis. JIMA 1983; 80: 140–1.
74. Zissis NP, Hatzioti AJ, Antoniadis D, Ninika A, Hatziotis J. Therapeutic evaluation of Levamisole in recurrent aphthous stomatitis. J Oral Med 1983; 38: 161–3.
75. Cho NJ, Choi DY, Son SJ. Therapeutic Effect of Levamisole in Recurrent Aphthous Stomatitis. Korean J Dermatol 1979;17(6):389-96.
76. De Cree J, Verhaegen H, De Cock W, Verbruggen F. A randomized double-blind trial of levamisole in the therapy of recurrent aphthous stomatitis. Oral Surg Oral Med Oral Pathol 1978;45:378-84.
77. Barrons RW. Treatment strategies for recurrent oral aphthous ulcers. Am J Health Syst Pharm 2001;58(1):41-50.
78. Kaplan B, Cardarelli C, Pinell SR. Double blind study of levamisole in aphthous stomatitis. J Oral Pathol 1978; 7: 400–4.
79. deMerieux P, Spitler LE, Paulus HE. Treatment of Behcet's syndrome with levamisole. Arthritis Rheum 1981;24(1):64-70.
80. Sampson D. Studies on levamisole, a potentially useful drug in the treatment of Behçet's syndrome. J Oral Pathol 1978;7(6):383-6.
81. Sun A, Wang YP, Chia JS, Liu BY, Chiang CP. Treatment with levamisole and colchicine can result in a significant reduction of IL-6, IL-8 or TNF-a level in patients with mucocutaneous type of Behcet's disease. J Oral Pathol Med 2009; 38: 401–5.
82. Lu SY, Chen WJ, Eng HL. Dramatic response to levamisole and low-dose prednisolone in 23 patients with oral lichen planus: a 6-year prospective follow-up study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995; 80: 705-9.
83. Chiang CP. Levamisole is an effective immunomodulator for patients with oral lichen planus. J Formos Med Assoc 2012;111:661.
84. Won TH, Park SY, Kim BS, Seo PS, Park SD. Levamisole Monotherapy for Oral Lichen Planus. Ann Dermatol 2009;21(3):250-4.
85. Sun A, Chia JS, Wang JT, Chiang CP. Levamisole can reduce the high serum tumour necrosis factor-a level to a normal level in patients with erosive oral lichen planus. Clin Exp Dermatol. 2007;32(3):308-10.
86. Lozada F, Silverman S, Cram D. Pemphigus vulgaris: a study of six cases treated with levamisole and prednisone. Oral Surg Oral Med Oral Pathol 1982; 54: 161-5.
87. Lozada-Nur F, Cram D, Gorsky M. Clinical response to levamisole in thirty-ninepatients with erythema multiforme: an open prospective study. Oral Surg OralMed Oral Pathol 1992; 74: 294-8.
88. Dhar S, Kanwar AJ, Ghosh S. Levamisole in erythema multiforme. Oral Surg OralMed Oral Pathol 1993;76: 678-9.
89. Ansarin H, Savabynasab S, Behzadi AH, Sadigh N, Hasanloo J. Doxycycline plus levamisole: combination treatment for severe nodulocystic acne. J Drugs Dermatol 2008;7(8):737-40.
90. Rassai S, Mehri M, Yaghoobi R et al. Superiorefficacy of azithromycin and levamisole vs. azithromycin in the treatment of inflammatory acne vulgaris: an investigator blind randomized clinical trial on 169 patients. Int J Clin Pharmacol Ther 2013;51(6):490-4.
91. Eskola J, Soppi E, Ruuskanen O, Fräki JE. In vitro Thymosin- and Levamisole-induced ıncrease of lymphocyte transformation in psoriatic patients. Arch Dermatol Res 1978:263:335-7.
92. Kocabas CN, Sekerel BE, Firat PA, Okur H, Adahoglu G. Levamisole: Might It Be used in Treatment and Prevention of Atopic Diseases? J Asthma 2004;41(5):547-51.
93. Chen LY, Lin YL, Chiang BL. Levamisole enhances immune response by affecting the activation and maturation of human monocyte-derived dendritic cells. Clin Exp Immunol 2008;151:174-81.
94. Zhang H, Shan C, Hua Z, Zhao P, Zhang H. Treatment of Chronic Idiopathic Urticaria with Levamisole: a Multicentre, Randomized, Double-blind, Controlled Trial. J Int Med Res 2009; 37: 1167-72.
95. Filo V, Galbavy S, Borecka D et al. Disseminated angiolymphoid hyperplasia with eosinophilia successfully treated with levamisol. J Dermatol Treat 2000;11: 269-72.
96. Yu J, Jin H, Kang H. A Case of Levamisole Treatment for Kimura's Disease Associated Nephrotic Syndrome. Korean J Nephrol 2011; 30: 315-20.
97. Lynn E. Spitler, Richard Sagebiel. A Randomized Trial of Levamisole versus Placebo as Adjuvant Therapy in Malignant Melanoma. N Engl J Med 1980;303:1143-7.
98. Sondak VK, Wolfe JA. Adjuvant therapy for melanoma. Curr Opin Oncol 1997; 9: 189-204.
99. Barth A, Morton DL. The role of adjuvant therapy in melanoma management. Cancer 1995;75(2):726–34.
100. McManus AT. Examination of neutrophil function in a rat model of decreased host resistance following burn trauma. Rev Infect Dis 1983;5(5):898-907.