Levamisole as an Experimental Immunomodulating Agent

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History of Levamisole

Tetramisole, the parent compound of levamisole, was discovered in Belgium in the early 1960's. Tetramisole was first marketed as a veterinary anthelmintic in Belgium in 1965. A year later it was introduced as a human anthelmintic in Brazil.

American Cyanamid scientists were successful in separating the optical isomers of tetramisole. The levorotatory isomer, levamisole, was found to be the active anthelmintic portion. The levamisole portion had a much wider margin of safety and lower dosages were required than for tetramisole.

Anthelmintic Activity

Levamisole has a very wide spectrum of activity, having high efficacy against more than 60 species of parasites in 13 animal species including man. Levamisole is currently marketed in more than 100 countries under several trade names. In the more than 10 years since its introduction, no known parasitic resistance has developed to levamisole.

Levamisole as an Immunomodulating Agent

Several clinical observations in man and animals in the late 1960's and early 70's, following the use of tetramisole as an anthelmintic, suggested some beneficial effect on host defense mechanisms. Gerard and Micheline Renoux (8) in 1971 first published on the effects of tetramisole on the host defense mechanism in mice. Mice were vaccinated with antibrucella vaccine (B19), challenged 42 days later with virulent *B. abortus* organisms and sacrificed 11 days later. *B. abortus* colonies were grown from the spleens of vaccinated mice suggesting incomplete protection. However, when tetramisole was administered 2 days after the B19 vaccine, the mice were fully protected. These observations by Renoux have subsequently been confirmed by many others. Since then, a wealth of data has accumulated regarding the immunomodulating effects of tetramisole and levamisole in a variety of animal species and man.

Several studies were initiated to determine if levamisole affected humoral or cellular immunity. The conclusions reached from these studies is that levamisole has little or no effect on humoral immunity (antibody production) in healthy subjects. The general conclusion is that levamisole often normalizes the functions of phagocytes and t-lymphocytes when their function is depressed. Stimulation of above-normal levels of cellular immune activity does not seem to occur and cells from normal animals and man are generally unaffected by levamisole treatment.

Large scale clinical research trials began in 1971 to test the effect of levamisole in all those human diseases that are either definitely or conceivably caused or accompanied by anergy or impaired cellular immune mechanisms. Because the preponderance of data is the result of human trials, we will present some data from these trials and follow with data from animal and poultry trials.

There unfortunately is not a great deal of data yet available from research in our common domestic species. This is especially true in the bovine. However, we have been advised of several interesting clinical observations regarding the use of levamisole in the bovine. These will be presented here with the understanding that the data is of a subjective nature for the most part and is not the result of strictly controlled studies.

Table 1

Levamisole Therapy for Rheumatoid Arthritis (5)

Levamisole (3 x 50 mg daily) at least as effective as D-penicillamine (1/4 to 1 g daily) and more effective than placebo in treatment of rheumatoid arthritis.

	Levamisole n=12	Penicillamine n=12	Placebo n=10
Pain	+++	+	-
Morning Stiffness	++	++	-
Joint Size	+++		-
technetium Index	++	+	-
Sedimentation Rate	+++	+++	-
Latex Titre	+++	+++	-
Ig G	++	+++	-
Ig M		++	-

Statistical significance of changes after 6 months' treatment.
+++ $p<0.01$; ++ $p>0.01$ <0.05; + $p>0.05$ <0.10; - $p>0.10$

Other experiments have shown that levamisole does not alter host resistance to primary invasion of pathogenic viruses, bacteria, or protazoa in immunologically competent subjects.

Recent trials in Brazil, using levamisole in broilers, vaccinated for Newcastle disease, and subsequently challenged with virulent virus, is of interest.

Dr. Irwin points out in this figure that there is a slight difference in the geometric mean sn titers at two of ten sampling points. This difference has a "significant tendency" ($p<0.02$) when using the binomial sign test but is not significantly different

Table 2

Levamisole in Upper Respiratory Tract Infections in Children (9)

	Treatment Levamisole 1.25 mg/kg B.I.D. 2 Days Each Week x 6 Months	Placebo
No. of Patients	38	32
Treatment Evaluation %		
Much Better	54	7
Better	35	36
No Change	11	50
Worse	0	7

Levamisole resulted in reducing number, duration and severity of disease ($p<0.001$).

Table 3

Levamisole Enhancement of Protection in the Immunologically Immature Rat (4)

Survival in suckling rats challenged with staphylococci or with herpes virus type 2.

Challenge	Treatment - Survival Levamisole 30 ug S.C. Day Before, Day of, Day After Challenge	Solvent
Staphylococci	36/40	1/21
Herpes Virus	26/63	0/62

Table 4

LOT A. Vaccinated NCD - 10 mg/kg levamisole via drinking water 24 hours post-vaccination. Birds vaccinated and treated at 7 and 30 days of age (3).

Hi Titers/ No. of Birds	Day 15	Day 30	Day 40	Day 60	Day 60 Challenge
1:5	0	0	0	0	
1:10	0	0	0	0	
1:20	0	0	0	0	32.5%
1:40	5	2	1	4	Mortality
1:80	32	8	11	28	
1:160	22	18	28	33	
1:320	19	19	33	11	
1:640	2	21	7	4	
1:1280	0	12	0	0	

Table 5

LOT B. Vaccinated NCD at 7 days and 30 days, no treatment with levamisole (3).

Hi Titers/ No. of Birds	Day 15	Day 30	Day 40	Day 60	Day 60 Challenge
1:5	0	0	0	14	
1:10	1	0	0	23	
1:20	22	8	15	28	
1:40	32	20	21	11	80%
1:80	23	24	18	4	Mortality
1:160	2	21	19	0	
1:320	0	6	7	0	
1:640	0	1	0	0	
1:1280	0	0	0	0	

($p<0.2$) using the students t test. Dr. Irwin also maintains that it is unlikely that this would effect the animal's capability to recover from or maintain resistance to IBR infection.

Dr. John Anderson at the University of Minnesota has used levamisole in a preventive medicine program at a dairy-beef operation over the last six months. On arrival all calves are given erythromycin

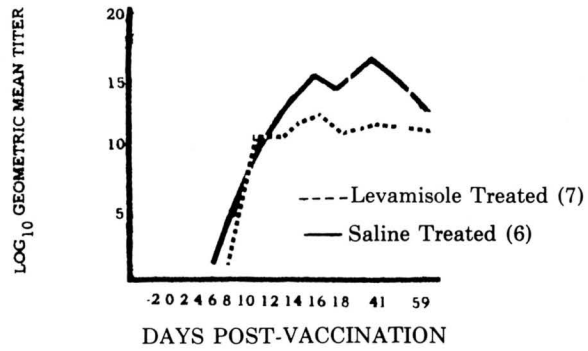

Figure 1. Geometric mean serum-neutralization titers in calves vaccinated against infectious bovine rhinotracheitis and simultaneously given levamisole (principals) or saline solution (controls) (6).

Table 6

Results of Immunotherapy with Levamisole (7)

Animal & Age	Clinical Condition	WBC	BVD	PHA	Results
Holstein, 2 yrs.	Post-surgical complications	●	+	●	Favorable
Hereford, 1 yr.	Acute BVD	●	+	●	No resp.
Hereford, 1 yr.	Same	●	+	●	No resp.
Hereford, 1 yr.	Same	●	+	●	No resp.
Holstein, 3.5 yrs.	Post-surgical complications	●	+		Favorable
Holstein, 2.5 yrs.	Post-calving complications	●	+	N.D.	Favorable
Charolais, 10 mos.	Chronic BVD	●	-	N	Favorable
Holstein, 8 mos.	Post-vacc. BVD	●	+	●	Favorable

Levamisole 1 mg/lb. daily until improvement then 3 consecutive days per 2 week period until complete recovery. Levamisole 1 mg/lb. 3 consecutive days/week until recovery.

Table 7

Levamisole in Young Calves (2)

No. Calves	Age	Treatment	Results
150	2 wks.	Erythromycin Ade Selenium Levamisole	Reduce Scours 50% +. Better Response To Treatment.

Table 8

Levamisole as Supportive Therapy in Mucosal Disease (1)

No. Cows	Age	Clinical Condition	Response
9	Adult	Mucosal Disease	3/9 Favorable

3 cc, ade 2 cc, selenium 1/2 cc, iron 5 cc, and .6 cc of levamisole daily x 3 days. Four days without treatment are followed by 3 more days of levamisole at the previous dosage level. Reportedly scours have been reduced by more than 50% in this operation. Dr. Anderson feels that response to treatment is improved also. After two weeks all calves are immunized with triangle 4, IBR, PI3 and pasteurella bacterin.

Dr. Leland Allenstein reports a favorable response to the use of levamisole in adult cows with acute mucosal disease complex. The dosage schedule used is the same as that employed by Dr. Johnson.

Summary

Levamisole is a highly efficacious anthelmintic marketed around the world for the treatment of internal parasites in animals and man. A large volume of data has been accumulated in the past several years regarding the immunomodulating effects of levamisole in man, laboratory animals, and to a lesser extent in our common domestic animals. Levamisole in general can be said to stimulate cell-mediated immunity in those subjects in which this system is depressed. Cellular immunity is adversely affected in a number of diseases in animals and man. Compounds which normalize the cellular immune system one day may play an important role in the management of these conditions. Humoral immunity in most studies has shown to be generally unaffected to any significant degree by the use of levamisole.

American Cyanamid markets levamisole under the trade names of Ripercol and Tramisol in the United States as an anthelmintic. Cyanamid offers this information as a report of research and clinical observations in various species. This should not be construed to imply an endorsement or recommendation for use of levamisole in other than an approved manner in species for which it is cleared.

Reference

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