Original Article

Dose and Time Related Effects of Lindane (γ-Hexachlorocyclohexane) on Hair Growth in Rabbit

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Abstract

Background: One of the most effective 2nd line scabicidal agent lindane (γ -HCH) is still used in many countries. It is moderately hazardous and causes severe physiological dysfunction in various organ systems. **Method:** The effects of (γ -HCH) on hair growth of male orytolagus Cuniculus Rabbit was studied in variable doses of 5,10,15 and 25mg/kg body weight for short term (up to 14 days) and also long term (up to 30 days) exposure. In addition general conditions and also some hematoenzymatic parameters were recorded in unexposed and exposed (treated) animals. **Results:** There was gradual increase in loss of hair with increasing dose of Lindane. With 5mg/kg body weight mild hair loss in neck and trunk, 10mg/kg body weight mild patchy loss of hair in neck & trunk region, 15 mg/kg body weight marked patchy loss of hair in neck region & moderate patchy loss of hair in trunk region, 20mg/kg body weight patches of almost complete loss of hair all over the body was observed. In addition, dose and time related anorexia, diarrhea, behavioral changes (weakness, restlessness, excitement and hyperactivity), bleeding tendency (observed while taking blood) and enzymatic changes (significantly increased serum alkaline phosphatase and SGPT) were also observed. **Conclusion:** The pharmacological use of γ-HCH, even as a 2nd line scabicidal agent should be strictly banned owing to its toxic effect on various systems of body. **Key words:** Lindane, scabicidal agent, hair growth, hematoenzymatic parameters.

INTRODUCTION

Lindane is man-made organochlorine, a chemical variant of hexachlorocyclohexane (HCH). Hexachlorocyclohexane (HCH) is a cyclic compound. The position of the Cl atoms gives this cyclic compound eight isomeric forms. The γ-isomer of hexachlorocyclohexane (γ-HCH) is a halogenated organic insecticide which at one time was used widely throughout the world.[1,2].

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It was first introduced as a scabicidal agent for human use in the 1950s [3] and later on it was used topically as a prescription medication for treatment of human infestations of head lice and scabies. [4] The WHO classified lindane as "Moderately Hazardous".[5] Lindane causes severe physiological dysfunction in various organ systems by enhancing oxidative stress by interacting with the cell membrane, triggering the generation of Reactive Oxygen Species (ROS) and altering the level of antioxidant molecules. [6,7,8].

A variety of adverse reactions to lindane pharmaceuticals have been reported ranging from

skin irritation, burning sensations, itching, dryness, rash, seizures and rarely death.[5,9] Exposure to large amounts of lindane can affect the nervous system, producing a range of symptoms from headache and dizziness to seizures, convulsions and more rarely death. [10,11,12] Prenatal exposure has been associated with altered thyroid hormone levels and affects brain development. [13]

In 2003, the FDA issued a "black box" public health warning for lindane treatments, reemphasizing that lindane should only be used as second line therapy. Second line of treatment means that it can only be used/prescribed when other "first line" treatment have failed or cannot be used.[14,15] The black box warning emphasizes that lindane should not be used on premature infants and individuals with known uncontrolled seizure disorders, and should be used with caution in infants, children, the elderly, and individuals with other skin conditions (e.g. dermatitis, psoriasis) and people who weigh less than 110lbs(50kg), as they may be at risk of serious neurotoxicity.[4]

MATERIALS AND METHODS

Fifty adult male rabbits (oryctolaguscuniculus of approximately same ages (9 months) were divided into groups A,B,C,D and E, each comprising of ten animals . Group A animals were kept as control, and given empty capsules. Group B,C,D and E animals were given lindane (γ -HCH) orally in capsules with the help of vaginal speculum. One capsule containing lindane with dose level 5,10,15 and 20mg/kg body weight was given once daily for 4 weeks to B,C,D and E group animals respectively.

Status of hair growth was observed during the experimental study on weekly basis in the morning before giving feed. In addition, general physical conditions, including behavioral changes and body weight of each animal were recorded. Blood samples from the marginal ear vein of each animal were collected weekly for some hematoenzymatic parameters.

RESULTS

Hairs of control group A animals were shiny, significant growth was noticed and there was no detectable hair loss up till the end of experiment.

Among group B animals, mild hair loss in neck region was noted during the 4th week of experiment. (Fig.1)

Mild but definite patchy loss on the trunk and neck regions was observed during last week in the C group animals. (Fig.2)

Detectable hair loss was seen during the 3rd week in group D animals over the trunk and neck regions, which became more marked and patchy toward the terminal stage of experiment. (Fig.3)

Detectable hair loss was observed even during the 2nd week in case of group E animals, that became marked and patchy during 3rd week (Fig.4) and in 4th week it was much more marked and diffused. (Fig.5)

Figure-1

External appearance of rabbit treated with 5 mg/kg (group B) of Lindane. Mild hair loss in neck & trunk region

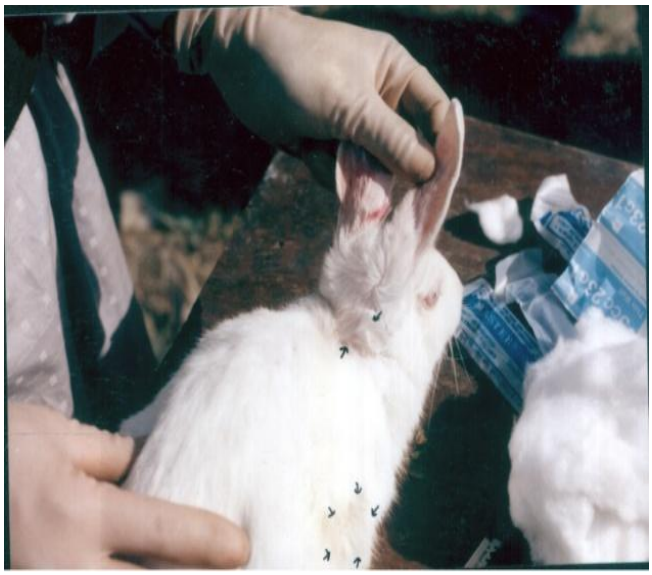

Figure-2
External appearance of rabbit treated with 10 mg/kg (group C) of Lindane. Mild patchy loss of hair in neck & trunk region

Figure-3
External appearance of rabbit treated with 15 mg/kg (group D) of Lindane. Marked patchy loss of hair in neck region & moderate patchy loss of hair in trunk region

Figure-4
External appearance of rabbit treated with 20 mg/kg (group E) of Lindane at the end of 3rd week. Marked & more diffuse loss of hair all over the body

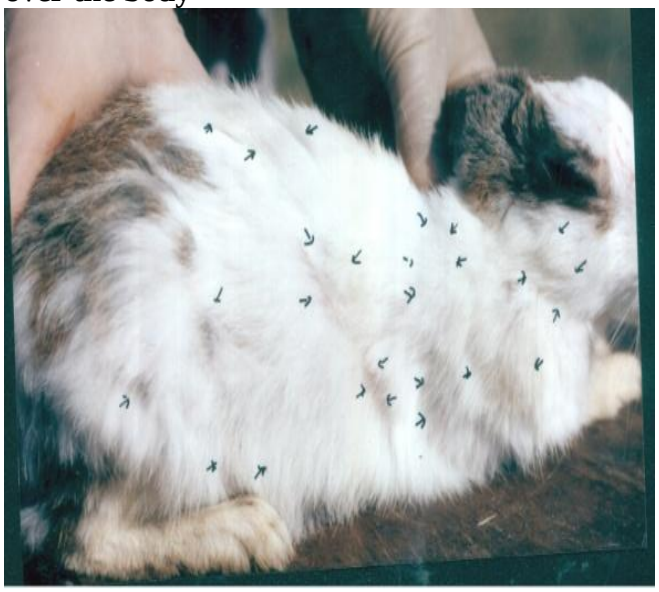

Figure-5
External appearance of rabbit treated with 20 mg /kg (group E) of Lindane at the end of 4th week. Patches of almost complete loss of hair on trunk

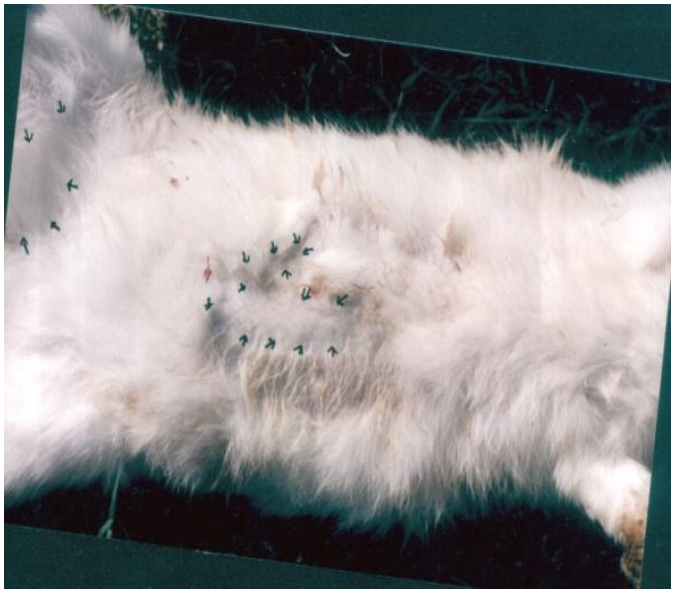

Table-1

Effect of Lindane (γ-HCH) on mean body weight of rabbit

Groups		Weight (kg) One Week	1st Week	2nd Week	3rd Week	4th Week	Growth rate (%again/day)
A	Mean	1.1423	1.1597	1.1970	1.2196	1.2432	0.2944
	± SE	0.0017	0.0015	0.0024	0.0024	0.0016	0.0061
B	Mean	1.2445	1.2511	1.2631	1.2697	1.2794	0.0935**
	± SE	0.0018	0.0028	0.0027	0.0035	0.0031	0.0101
C	Mean	1.2700	1.2750	1.2729	1.2707	1.2651	-0.015***
	± SE	0.0030	0.0037	0.0034	0.0036	0.0029	0.0050
D	Mean	1.3700	1.3570	1.3309	1.3410	1.3200	-0.121***
	± SE	0.0035	0.0033	0.0034	0.0083	0.0021	0.0061
E	Mean	1.3900	1.3840	1.3730	1.3510	1.3000	-0.216***
	± SE	0.0033	0.0036	0.0032	0.0036	0.0033	0.0113

For statistical significance control group has been compared to treated group.

Student's t-test (P<0.05=*, P<0.01=**, P<0.001=***)

Graph showing the effect of lindane (ϒHCH) on growth rate of rabbit.

Figure-6

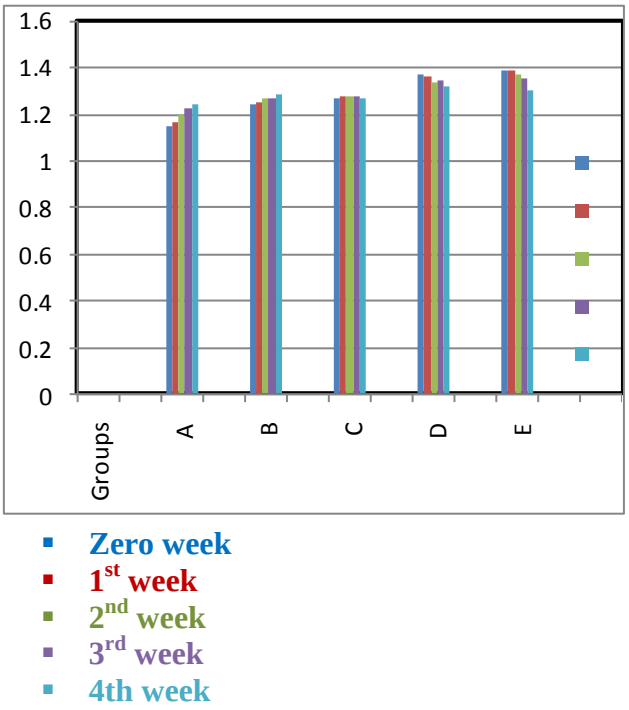

Table-2

Dose related effects of Lindane (γ HCH) on some hematoenzymatic parameters of rabbit

	Serum Alkaline Phosphatase U/I				Serum Glutamic Pyruvic Transaminase U/I			
Group	1st week	2nd week	3rd week	4thweek	1stweek	2ndweek	3rdweek	4thweek
A	49.13±1.0	50.25±0.3	50.30±0.23	49.80±1.5	41.87±1.30	40.25±0.8	40.50±1.18	40.25±0.98
B	52.0±2.08	53±0.47	54.50±0.54	*57±0.63	41±0.44	43±0.82	*45±0.64	**50±1.05
C	55.0±0.86	*57±0.64	*60±1.22	**70±1.26	43±0.53	*45±1.05	**55±0.59	**60±1.22
D	*60.0±1.22	**80±1.06	**100±1.07	**110±1.26	*45±1.01	**50±0.42	**60±1.43	**69±0.39
E	*62.0±0.44	**85±0.66	**104±0.81	**114±0.73	**47±0.42	**52±0.53	**65.05±0.74	**79.5±0.42

For statistical significance control group has been compared to treated group/student's t-test (p<0.01*=p<0.001**)

PHYSIOLOGICAL CONDITIONS

Group A animals were generally healthy and active. Mild degree of restlessness and hyperactivity were noticed among group B animals during the last 4th week of experiment.

Mild degree of weakness, restlessness, excitement, hypersensitivity and reactivity were observed during 3rd week among C group animals, and these changes become more apparent at the end of 4th week.

In group D animals behavioral changes were realized even at the end of 2nd week, and these became more significant towards the end of experiment.

The behavioral changes were apparent even during early 2nd week among the E-group animals, and these became much more significant during 3rd week, and towards the end of experiment marked weakness, restlessness, excitement, hypersensitivity and hyperactivity were observed in all animals of the Group E

GIT Disturbances

No observable change was noticed regarding food intake in group-A animals.

Reduced food intake (anorexia) and mild diarrhea was noticed among the group-B animals during 4th week of experiment.

There was dose and time related anorexia and diarrhea in group C, D and E animals during the experimental study period.

Body Weight

In group A animals, there was generalized trend towards gain in body weight and at the end of experiment all animals gained significant body weight.

There was insignificant increase of body weight among the group-B animals at the end of experiment.

There was slight decrease in body weight of C-group animals at the end of experiment.

There was significant decrease in body weight of D-group animals and this decrease was more significant in Group-E animals at the end of study (Table-1)

Hematoenzymatic Parameters

All parameters investigated remained constant in control group A animals throughout the experiment.

Serum alkaline phosphatase and SGPT level were increased significantly even in 1st week. Further increase followed in dose and time related/dependent pattern and at the end of experiment significant increase was observed even in lowest dose treated group-B animals (Table-2)

There was also dose and time related bleeding tendency that was noticed while taking blood samples.

DISCUSSION

Hair loss

This could be due to the deposition of lindane (γ - HCH) subcutaneously damaging the hair follicles [16] and since, γ -HCH has strong tendency to deposit subcutaneously [17], it could directly damage the hair follicle, thence the hair loss.

Decreased blood supply to hair follicle caused by damage to blood capillaries could be the other cause of hair loss. [18]

Behavioral Changes

These changes could be result of direct drug action on CNS.[17]

Lindane is a neurotoxin that interfering with the GABA receptor-chloride channel complex, [19,20,21] could produce a range of symptoms from headache and dizziness to seizures, convulsions and more rarely death. [10,11]

GIT Disturbances

Lindane has direct action on the satiety center in CNS [17] and it is also excreted in saliva with very nauseating metallic taste [22], thus causing the loss of appetite (anorexia).Diarrhea could be due to direct action of lindane on Enteric Nervous System of the GIT. [17]

Body Weight

The cause of reduced weight could be due to anorexia [23], enhanced protein degradation along with decreased synthesis and GIT disturbances.[24]

Hematoenzymatic Changes

Lindane has been found to increase lipid per oxidation (LPO) and decrease glutathioine (GSH) level, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione S-transferase (GST) , glutathione reductase (GR), quinine reductase activity and protein.[25]

The level of serum alkaline phosphatase is always considered to be the index for obstructive and degenerative hepatic disease. Increase serum levels of transaminase (SGPT & SGOT) have been described to be associated with cell necrosis of many different tissues. [26]

Liver is a metabolically versatile organ responsible for the regulation of internal chemical environments [12,] the primary site for detoxification [5] and it is major organ of antioxidant defense system[27]. Lindane hepatotoxicity would be reflected by wide variety of changes in serum level of alkaline phosphatase, SGPT and SGOT. [26] In this study, lindane proved to be a highly toxic chemical that produced variety of changes even with smaller (5mg/kg of body weight) dose. Since it is a persistent pollutant [1] and further it can get into body by oral route (eating lindane contaminated food like plants, meat and dairy products), pulmonary route (breathing in work places) and through skin (through use of soaps, lotion, or shampoo containing lindane, that help treat and control head and body lice and scabies) [28]. The chances of accumulation in body fat and subsequent toxicity are more in/among communities in the developing countries(like Pakistan),where the environmental protection and food and drug administration agencies might not be as effective as in developed countries.

CONCLUSION

Lindane is highly toxic. Keeping in view of its highly toxic nature and its rapid absorption through all major routes [28] (oral, pulmonary and skin), its (lindane) use as a pesticide must be strictly banned (as in developed countries) [4] and its pharmaceutical use must only be allowed under strict medical advice.

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