

Original Research Article**DOSE TITRATION, EFFICACY AND SAFETY OF 'DROP ON' IVERMECTIN FOR THE MANAGEMENT OF KNEMIDOCOPTES SPP INFESTATION IN BUDGERIGARS.****MD Kamal Hossain*^{ab}, Daniel Sanderson^a, Kamrun Nahar^a, Dr AW Gestier^a, Mohammad Salahuddin Khan^c and Kaiser Hamid^d**^aVetfarm Pty Ltd. R&D Centre, Wagga Wagga, NSW 2650, Australia.^b School of Biomedical Science, Charles Sturt University, Wagga Wagga, NSW, Australia^c Department of Pharmacy, Jahangirnagar University, Savar, Dhaka 1342, Bangladesh^d University of Sydney, NSW, Australia.**ABSTRACT**

The objective of the study was to evaluate the treatment efficacy and safety of Ivermectin 'drop on' liquid for the management of Knemidocoptes infestation in Budgerigars. Budgerigars (*Melopsittacus undulatis*) were selected as representative of caged birds, being the most commonly affected species. Fifteen (15) birds for dose titration, eighteen (18) for efficacy and nine (9) for the safety study were used. The efficacy study was conducted over three weeks. Birds of bodyweight less than 30 g was given one drop and birds of bodyweight 30 g to 100 g was given two drops of ivermectin solution (Avimec^(R)) on the skin of the thigh and treatment was repeated weekly. The safety study was performed as an acute toxicity trial with a single application. 0.1 % ivermectin 'drop on' liquid was effective for the eradication of mite within two weeks. One drop (0.05mL) was effective for birds of bodyweight of less than 30g and two drops (0.1 mL) was effective for birds of bodyweight 30g to 100g. Significant improvement was observed after day 7 and complete eradication was observed within 2 weeks. For the safety study, birds were treated 5X and 10X of the standard dose. No adverse reaction or toxicities were observed. Topical "drop on" ivermectin liquid (Avimec) showed rapid and effective treatment of Knemidocoptes infection. Moreover 0.1 % ivermectin drop on liquid also demonstrated a high therapeutic index of greater than 10X of standard dose.

Key Words: Ivermectin, Scaly face, Drop On, Budgerigars.

***Corresponding Author:** MD Kamal Hossain, School of Biomedical Science, Charles Sturt University, Wagga Wagga, NSW, Australia. Email: hossain_238@yahoo.com**INTRODUCTION:**

"Scaly face" is an infestation by burrowing mites (*Knemidocoptes pilae*, also called *Cnemidocoptes pilae*). It is frequently encountered in small psittacine birds, where the mite affects featherless tracts, most commonly the beak, cere, eyelids and vent ^{1,2}.

Lesions develop and spread slowly and there is no pruritus. Cage birds may develop the lesions after having appeared normal for many months. The typical case develops in young adult birds. Advanced infestations have lesions on the beak, cere, eyelids, and vent. As the lesion worsens, the beak becomes distorted and bizarrely shaped due to an increased growth rate in the bed of the beak.

Ivermectin is the drug of choice to treat knemidokoptosis³. It can be administered orally, topically or intramuscularly with equal efficacy. Ivermectin is a mixture of two avermectins (22, 23 dihydroavermectin B1a and 22, 23 dihydroavermectin B1b), which are members of a new class of macrocyclic lactones derived from *Streptomyces avermitilis*. This class has broad spectrum anthelmintic and insecticidal activity. Ivermectin has been used safely in horses, dogs, cattle, pigs, birds, sheep and human beings with efficacy against many adult and larval nematodes, lice, and mites⁴⁻⁹.

Ivermectin has been used widely for many years, in a range of dosages and methods of application in avian species such as Budgerigars, Canaries, Passerines, Raptors and Pigeons. Intramuscular delivery of ivermectin to small birds may be toxic and oral administration may be practically difficult for the owner, and so topical “drop on” liquid may be a suitable alternative.

The present study was conducted to evaluate the efficacy and safety of ivermectin “Drop on” liquid to budgerigars.

MATERIALS AND METHODS

Experimental protocols were developed for testing safety and efficacy of ivermectin drop on liquid according to the Australian Pesticides and Veterinary Medicine Authority (APVMA) drug approval program.

Birds

Budgerigars, as representative of the small psittacine target group were used for the clinical trial. The study was conducted at the Vetafarm Research Centre. Birds were sourced from breeders and Pet Stores and acclimatised to new caging for seven days prior to treatment. Birds were fed normal diet of commercial budgerigar seed (Avigrain, Avigrain Australia, PO Box 5397, Chittaway, and NSW 2261) and had free access to water. Microscopic examination of scrapings before the start of the study was conducted to confirm the presence or absence of mites.

Treatment formulation and dose

Ivermectin ‘drop on’ liquid solution containing 0.1% (1000 µg/ml) (Avimec, Vetafarm Pty Ltd, Australia) and 0.01% (100 µg/ml) w/v ivermectin solution were used as test drug. Avimec is designed for topical application as a drop, and each drop delivers 0.05 mL of ivermectin solution. One ml normal syringe was used for accurate delivery of each drop.

Dose determination: To test the efficacy, Avimec 50 ug / 30g bird, a slight higher than the allometrically determined dose (22.4 - 35 ug/30g Bwt) was administered^{10, 11}. Prior toxicity trials showed a safety margin of >10x the therapeutic dose, allowing a slight over-application of the therapeutic dose

Dose Titration Study

0.01 and 0.1% Avimec were used to determine the effective dose of ivermectin drop on liquid on budgerigars, 15 birds being used in the trial. Cere scrapings from the clinically affected birds were collected, dispersed in paraffin oil and examined by light microscopy to determine mite infestations prior to the treatment. Mite infestations were confirmed by the presence of one or more moving mite per scraping.

All treated birds were observed hourly for the first six hours and then daily. Seven days after treatment, a repeat scraping from the cere was collected and examined to assess the presence or absence of active mites. The study was conducted for three weeks. Mite eradication was achieved by the second week but a follow up scraping from the cere was performed at three weeks to reconfirm eradication

Birds were divided into 5 different groups having three birds in each group:

Group A was given 2 drops of carrier solution without the Ivermectin,

Group B was given 1 drop of 0.01 % Ivermectin to the birds weighing less than 30g,

Group C was given 1 drop of 0.1 % Ivermectin to the birds weighing less than 30g,

Group D was given 2 drops of 0.01 % Ivermectin to the birds weighing 30g -100 g,

Group E was given 2 drops of 0.1% Ivermectin to the birds weighing 30g -100 g.

Efficacy of treatment was determined on the basis of reduction in the appearance of mite on the cere scraping from the birds.

On days 7, 14 and 21 post treatments, the birds were assessed for evidence of infection by scraping of the cere area and microscopic examination of the scraping for the presence of *K. pilae*.

Efficacy Study

Avimec 0.1% solution was used. Eighteen budgerigars were used in the trial. All the birds had naturally acquired infestations. Cere scrapings were collected and examined by light microscopy to confirm mite infestations prior to the treatment.

After treatment, the birds were observed hourly for the first six hours and then daily. Seven days after treatment, a repeat scraping was collected and examined to check for the presence of mites. Scrapings were repeated on days 14 and Day 21 and examined as above.

Birds were divided into three groups:

Group A received two drops of carrier solution without Ivermectin.

Group B received one drop of ivermectin solution to the birds weighing less than 30 g.

Group C received two drops of ivermectin solution to the birds weighing 30 to 100g.

On days 7, 14 and 21, the birds were assessed by having a cere scraping examined by microscopy for the absence/presence of *K. pilae*.

Safety Study

For the safety study, 9 birds were divided into 3 groups.

Group I received 10 x the placebo solution (1 mL per bird),

Group II received 5X dose of ivermectin solution (0.5 mL per bird),

Group III received 10X dose ivermectin solution (1 mL per bird).

The large dose of liquid used in the toxicity trial was spread evenly over the skin of the chest and thigh of the birds using a 1 mL normal syringe. Both skin reaction and neurological effects were observed. In case of skin reaction, different stages of erythema and eschar formation and oedema formation were assessed. For neurological effects, ataxia, depression, lethargy, mydriasis, recumbency, tremors and death were assessed. The severity was scored from 0 to 4 in case of skin reaction. The severities of neurological effects were assessed as mild, moderate or severe.

Results

Clinical signs

The ivermectin formulation was tolerated with no systemic signs or local reactions. No birds were removed from the study for any reason.

Safety

Budgerigars were treated with the 5X and 10X of the standard dose to demonstrate the safety margin of the proposed dose and mode of application. None of the treated birds had any physical or behavioural reaction to the drug at the 10X of standard dose. The bodyweights varied between the groups but were considered not statistically significant ($P > 0.005$) (Table III). The body weights of birds treated with 10x Avimec appeared to be unaffected.

Effective Concentration

The 0.1% ivermectin drop on liquid was effective for the removal of mites within two weeks. Results are summarized in table I. Based on the dose titration result the 0.1% ivermectin was selected for further efficacy and safety studies.

Efficacy

Significant decrease in the appearance of mite in group B and C was recorded as compared to Group A (untreated control). Ivermectin 'drop on' liquid was effective at a single dose of one drop (birds weighing less than 30 grams) to two drops (birds weighing 30 – 100 grams) of 1000 µg/ml in treating knemidocoptes infestation in budgerigars. Significant improvement observed after one week treatment and complete removal of mite was observed after two weeks treatment.

Results are summarized in table II. No side effects were observed in any bird of any group. The results revealed that ivermectin was very safe and effective for the management of knemidocoptes in budgerigars.

Discussion

The present study was conducted to evaluate the efficacy and safety of topical ivermectin liquid in the treatment of scaly face mite infestation in the budgerigar.

The high efficiency of topical ivermectin for the management of mite infection is widely reported^{12, 13, 14}. Ivermectin dosage for passerine and small psittacine birds for topical application is reported as a 0.2 % solution (in propylene glycol); the pigeons: 0.5 ml applied topically to bare skin using 0.02% solution q7-14 d and for birds 200 µg/kg i.m., s.c., p.o. q7-14d¹⁵. Present study finding is also consistent with the previous study results. In this study one/two drop of ivermectin 1000 µg/ml 'drop on' liquid was effective for the management of scaly face

Evidence of ivermectin toxicity was not found in birds treated with 5 or 10 times than the recommended dose. A scoring system was introduced ranging from 0 to 4 to assess the skin reaction and mild moderate severe to assess the neurological condition. 12 birds were treated and no reports of adverse reaction or infection at the application site suggesting 0.1 % ivermectin drop on liquid is safe for budgerigars. Safety studies on ruminants (cattle and sheep) have indicated that test dose as high as 20 to 30 times of the recommended dose produced no ill effects¹⁶.

Conclusion: Under the present protocol conditions, the repeated use of ivermectin liquid formulation produced no noticeable adverse reaction in birds, nor was any reaction noted in the birds subject to the toxicity trial.

Results show that one treatment of Avimec removed mites from the cere of budgerigars in 14 days.

Table I Dose titration study results

Number of birds positive/ total number of birds

Group	Day 0	Day 7	Day 14	Day 21	% improved
Group A (Placebo)	3/3	3/3	3/3	3/3	0
Group B	3/3	3/3	2/3	2/3	33.33
Group C	3/3	0/3	0/3	0/3	100
Group D	3/3	3/3	3/3	2/3	33.33
Group E	3/3	0/3	0/3	0/3	100

Table II Efficacy study results

Number of birds positive/ total number of birds

Group	Day 0	Day 7	Day 14	Day 21	% improved
A (Placebo)	6/6	6/6	6/6	5/6	16.6
B	6/6	2/6	0/6	0/6	100
C	6/6	1/6	0/6	0/6	100

Table III

Mean bodyweight of different groups of birds and their differences during safety study

Groups	Mean bodyweight (g) (30-100g)		Differences(g)	Mean bodyweight (g) (<30g)		Differences(g)
	Day 1	Day14		Day 1	Day14	
Group I	230.9	257	26.1	107.1	112.2	5.1
Group II	221.8	242	20.2	110.5	115	4.5
Group III	202.5	227	24.5	109	113.75	4.75

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