Safety, efficacy, and tissues residues of ivermectin in reindeer

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Abstract: Safety, efficacy, and tissue residues of ivermectin, a broad spectrum parasiticide, were determined in Alaskan reindeer (*Rangifer tarandus*). Reindeer treated at 5 times and 10 times the standard dose of 200 mcg/kg had no detectable physical or behavioral reactions to ivermectin injected subcutaneously in the mid-cervical area. Ivermectin eliminated essentially 100% of reindeer warble larvae (*Hypoderma (Oedemagena) tarandi*). Tissue levels of ivermectin in back fat, injection site, muscle, liver, and kidney collected 3, 10, 17, and 24 days post injection were determined. All tissues levels rapidly declined and were approaching low unmeasurable amounts at the end of the 24 day test period. Ivermectin is a safe effective parasiticide that has been used successfully to threat thousands of reindeer in Alaska.

Key words: Reindeer, ivermectin, warbles, treatment, drug

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Introduction:

Reindeer (*Rangifer tarandus*) are not indigenous to Alaska. They were imported in 1892 from Siberia for use by the Eskimos. At the present time, reindeer in Alaska number approximately 30.000. Renewed interest in the Alaskan reindeer industry over the past 20 years has resulted in a moderate increase in animals. Concern was expressed by the Reindeer Herders' Association over the impact of warbles (*Hypoderma (Oedemagena) tarandi*) and nasal bots (*Cephenemyia trompe*) on the health and productivity of their herds. In Alaska, these parasites cause very severe infestations. Up to 2.000 warble larvae have been counted on the back of one reindeer, and numbers in the range of 500 to 1.000 are common. Herders described finding groups of 35 to 40 reindeer dead in late May with the only visible lesions being massive warble infestations, extreme emaciation, tissue necrosis, and loss of skin from the back. Herders also commented on the smaller size of fawns nursing heavily infested females, and that heavily infested yearlings were noticeably smaller in size than lightly infested cohorts. Reindeer owners complained about difficulties in herding reindeer being harassed by warble and nasal bot flies. The unwanted movement of reindeer from areas of good range to less desir-able beach or windy hillside areas was observed during periods of insect harassment (Dieterich, 1981).

Safety, efficacy and tissue residues of ivermectin, a broad spectrum parasiticide, were tested to determine the suitability of using the product to control warble and nasal bots in reindeer in Alaskan herds (Chabala, 1980; Campell, 1984; Bowie, 1986). This report describes field and laboratory studies carried out to gain ap-

proval by the United States Food and Drug Administration (FDA) for use of ivermectin in reindeer. Observations in this report are limited to the effects of ivermectin on warble larvae populations, but ivermectin was also used to concurrently threat reindeer nasal bots and internal parasites. Approval for the use of ivermectin in reindeer used for human consumption was obtained in 1985.

Materials and methods

Experimental protocols were developed for testing safety, efficacy and tissue residues of ivermectin in reindeer that would conform to the FDA drug approval program. As instructed by FDA, efficacy studies were limited to the effect of the drug on warbles as the presence or absence of the warble parasite could easily be determined by inspection of the skin of live reindeer in the late winter months.

Safety

Seventeen reindeer were injected with ivermectin and 8 reindeer served as controls. Animals were grouped on the basis of age, sex, and general condition to make treatment groups as comparable as possible. All test reindeer were held in a 2 hectare double-fenced pen with adjacent handling facilites. Diet consisted of available brom grass and a grain mixture (Quality Texture[1]) fed ad libitum.

A dosage of 200 mcg/kg was established as a standard dose based on data available for the use of ivermectin in cattle. Accordingly, 5 fawns (4 months of age) and 8 adults were injected subcutaneously in the mid-cervical area with 1000 mcg/kg ivermectin (5 times standard dose). Additionally, 4 adults were dosed with 2000 mcg/kg ivermectin (10 times standard dose) using the same protocol. Eight adult controls were injected with the same solution minus the active ivermectin ingredients. All test animals were osberved hourly the first day, four times daily the second day, three times daily the third day, and twice daily for the remainder of the period. Each time the animals were handled, the injection site was palpated and the general physical condition noted. Blood was collected for complete blood counts (CBC) before injection on day 0 and additionally on days 3,7,11,17,24 and 31 post-injection (PI). Body weights were taken at the time blood was collected.

Efficacy

The efficacy of ivermectin against the reindeer warble was tested in two trials. The first was a pilot study using 40 reindeer injected with the standard dose (200 mcg/kg) on January 31, 1981. These reindeer and 159 non-treated controls were part of a herd near Kotzebue, Alaska. Three treated reindeer were necropsied early in the study to visually assess the effect of the drug on warble larvae. The number of warbles on the remaining animals were counted by digital palpation at the end of the study on June 2, 1981.

A second efficacy study was carried out near ard dose of ivermecting (200 mcg/kg) and another 145 reindeer injected with the drug vehicle only. One hundred seventy one of the 316 treated reindeer were recovered in early June 1983. An assessment of body condition (1=poor, 2=average, 3=excellent) and a count of warble larvae by digital palpation was made during the month of June. An average number of warble larvae for treated and control reindeer was calculated.

Both test groups ranged freely with controls on western Alaska tundra ranges. These groups were mixed with reindeer herds that numbered from 4 to 7 thousand animals. The conditions they experienced were typical for reindeer in Alaska.

Tissue residues

The temporal dynamics of ivermectin tissue residues in reindeer were determined to esta-blish a withdrawal time after treatment which would result in acceptable residue levels. This study was started December 18, 1982 when a group of 145 reindeer was injected with the standard dose of ivermectin (200 mcg/kg) subcutaneously in the mid-cervical area. These reindeer were part of the large test group of animals used in the efficacy study. Two or 3 of these treated reindeer were shot on days 3, 10, 17 and 24 PI and tissues collected for analysis. Liver, muscle,

[1] Quality texture, Fisher Mills Inc., Seattle, WA, USA.

kidney, injection site, and back fat samples were collected in duplicate from treated and control animals, wrapped in aluminium foil, and frozen immediately.

Residue analyses were carried out at the University of California, Davis using the regulatory fluorescence/liquid chromatographic method developed by Merck & Co. (NADA #128-409)[2]. First order rate constants of elimination of ivermectin residues from reindeer tissues were calculated using a commercial kinetics program (RSTRIP)[3].

Results

Safety

None of the treated reindeer had any detectable physical or behavioral reactions to ivermectin. Control and treated reindeer had blood and body weight measurements that were essentially parallel. Males lost weight because of rut behaviour in both control and treated groups. One reindeer in each group had elevated white blood cell numbers due to unrelated infections. The injection sites were non-reactive.

Efficacy

Twenty six of the 40 treated reindeer in the first trial near Kotzebue were rounded up in June and examined to determine drug efficacy. These 26 treated reindeer had an average of 2 warble larvae per animal. All warbles were dead and undergoing absorption in the 3 treated reindeer necropsied earlier in the trial.

One hundred seventy-one of the 316 treated reindeer in the second trial near Nome were examined in June 1982. These 171 treated reindeer had an average of 4 warble larvae per animal.

Differences in the number of warble larvae in both trials of treated verses non-treated controls were significant at the $P < 0.001$ level using the student's t test. General body condition improved in treated reindeer which were subjectively compared to non-treated controls.

Tissue residues

Residues of ivermectin expressed as parts per million in back fat, injection site, muscle, liver and kidney were averaged from reindeer tissues

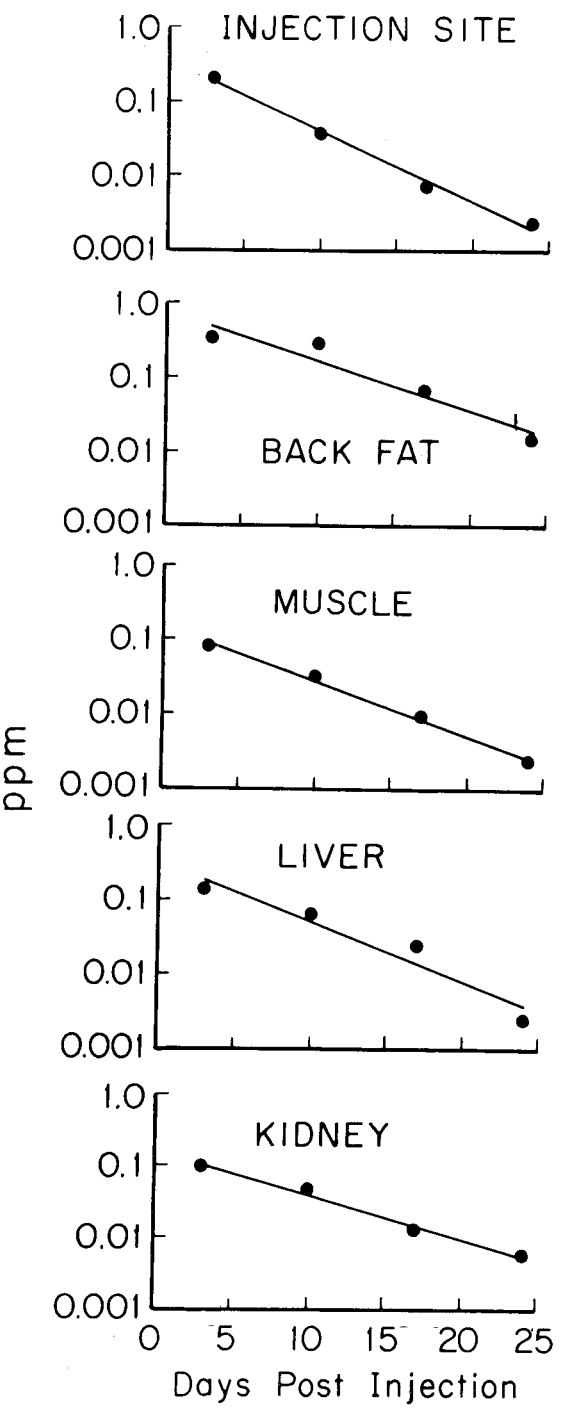

Figure 1: Residues of ivermectin in reindeer tissues after subcutaneous injection of 200 mcg/kg body weight. Each point represents the average concentration found in tissues.

[2] Merck & Co., Rahway, NJ, 07065, USA.

[3] MicroMath Software Co., Salt Lake City, Utah, USA.

collected 3, 10, 17 and 24 days PI (Fig. 1). Back fat had the highest levels of ivermectin present after injection when compared to the other tissues. All tissue levels rapidly declined and were approaching undetectable levels at the end of the 24 day test period. The time in days for 1/2 of the ivermectin to leave each tissue were: back fat, 7.1; injection site, 2.9; muscle 4.9; liver 5.8; and kidney, 5.7.

Discussion

No evidence of ivermectin toxicity was found in reindeer treated with 5 or 10 times the standard dose of 200 mcg/kg. Approximately 50.000 reindeer have been treated with ivermectin in Alaska over the past 5 years with no reports of adverse drug reactions or infections at the injection site. Most of these treated animals were not closely observed after being injected, but obvious illnesses or lesions would have been observed if they had occurred. Safety studies in other ruminants (cattle and sheep) documented test dosages as high as 20 to 30 times the standard dose produced no ill effects (Campbell and Benz, 1984).

Ivermectin is highly effective in controlling warble infestation in reindeer (Nordkvist *et al.*, 1984). The standard dose of the drug eliminates essentially 100% of the warble larvae (Nordkvist, *et al.*, 1983). In the current efficacy trials, there were a few animals treated that had warble larvae present. These animals may not have received the complete dose because cold temperatures and dense hair coats at the time of treatment made accurate administration difficult. Ivermectin effectively removes many species of parasites in domestic animals. Although effective anthelminthic spectrum of ivermectin in reindeer was not monitored in this study, samples collected from reindeer for clinical diagnostic purposes suggests that ivermectin has the same general effectiveness on reindeer parasites as it has on cattle parasites. Ivermectin has been found to be very effective as a parasiticide in other cervidae as well (Bowie, 1986).

Post-injection tissue residues of ivermectin decreased rapidly during the 24 days of the study. Back fat residues were initially nearly twice as high as residues in liver, injection site, muscle, or kidney tissue. However, residues in all tissues tested approached zero by day 24. Based on these data, the FDA established a 56 day withholding period. Therefore, in the USA, reindeer injected with ivermectin must not be slaughtered and used for human consumption within 56 days of treatment.

In cattle and sheep, liver is the tissue in which the drug is most persistent while in reindeer, the drug persists longer in fat. The time for 1/2 of the ivermectin to leave cattle liver was 4.9 days compared to 7.1 days to leave reindeer fat at the same dosage rate (Tway *et al.*, 1981).

Subjective evidence is available on the overall benefits of using ivermectin in Alaskan reindeer. Herders and researchers have observed larger yearlings, fawns and adults after ivermectin administration. Less insect harassment the summer following treatment has been reported by herders. Ivermectin is a safe effective parasiticide that has been and will continue to be a benefit to the reindeer industry.

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