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Efficacy of Weekly 0.1% Amitraz Dip with 4% Chlorhexidine Shampoo on Juvenile Onset Generalized Pyodemodicosis Unresponsive to Ivermectin Therapy in Japanese Chin Dog

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Abstract: A case of juvenile onset generalized demodicosis of one year old, intact female Japanese Chin dog weighing 3.1 kg was presented to the Small Animal Clinic of the College of Veterinary Medicine of Kyungpook National University. The diagnosis was made based on the physical examination, deep skin scrapings, hematology, serum chemistry, endocrinologic evaluation and bacterial culture. Numerous *D. canis* mites of various stages were observed in multiple skin scraping samples. CBC, serum chemistry, T_3, T_4 and free T_4 values were within normal range and *Staphylococcus intermedius* was isolated in bacterial culture of pustules. The dog was healthy other than skin lesions at the presentation. The three different treatment protocols were tried for the case. No clinical improvement was observed during 13 weeks of orally given daily basis ivermectin therapy at 600 μg/kg and 2 weeks of spot-on weekly basis selamectin therapy at 30 mg/kg with cephalexin given orally twice a day at 25 mg/kg. However, a remarkable remission was seen by 0.1% amitraz dip on weekly basis with 4% chlorhexidine bath given twice a week. The secondary staphylococcal infection and accompanied pruritus was almost disappeared in two weeks and she was recovered clinically normal in 9 weeks of therapy. The therapy was continued for 4 more weeks to prevent relapse. The dog is clinically normal and being monitored for development of any abnormal dermatological signs for the time being.

Key words: generalized demodicosis, amitraz, ivermectin, selamectin, dog

Introduction

Canine generalized demodicosis (CGD) is the sixth most common skin disease of dogs in North America[29]. It is a non-contagious, inflammatory parasitic dermatosis characterized by excessive proliferation of the commensal mite *Demodex canis* within the hair follicles and sebaceous glands [5,10,11,15,25].

Historically, canine generalized demodicosis has been a very frustrating disease to manage with a guarded prognosis. Due to the complicated nature of the disease, many treatment protocols have been developed. They include licensed acaricidal treatment protocol with amitraz at 250 ppm biweekly[25,26], off-label protocols at higher concentrations up to 1250 ppm with different frequencies[4,8,9,13], systemic macrocyclic lactones including milbemycin oxime[7,16,15], iver-mectin[6,14,18,19,23,26] and moxidectin[2].

There have been many reports about the efficacy of the off-label protocols of amitraz but the results of each study was varying with great discrepancy according to the different protocols, case selection and different criteria for cured cases, including long-term follow up periods. In Europe, weekly applications of amitraz at concentrations of 500 to 1000 ppm were reported to be very effective and safe in the treatment of CGD[4,12]. Thus the purpose of the present clinical case report was to evaluate the efficacy of the 0.1% weekly basis amitraz dip in the treatment of juvenile onset generalized demodicosis.

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Case Report

A 1 year old, intact female Japanese Chin dog weighing 3.1 kg was presented to the Small Animal Clinic of the College of Veterinary Medicine of Kyungpook National University with typical signs of chronic, juvenile onset, generalized demodicosis with secondary superficial pyoderma. Physical examination at three months of age had revealed that the signs of juvenile onset, localized demodicosis, which were focal alopecia limited to face, excessive scaling. The lesions spread as the patient grew up.

The patient had been treated for *Malassezia* dermatitis and ear mite previously at a local clinic but never been treated for demodicosis. At the presentation to our clinic, diffuse alopecia with variable erythema, silvery-grayish scaling, papules, severe pruritus, pustules, lichenification and crust were seen all over the body including the feet. The dog was healthy other than dermatological symptoms.

Microscopic examination and hematological examinations were performed for diagnosis. Skin scrapings from various sites including feet and ears contained numerous *D. canis* mites and various stages of development. A bacterial culture from pustules yielded coagulase-positive *Staphylococcus intermedius*. CBC, serum chemistry and thyroid profiles had no remarkable findings.

The dog was given cephalexin at 30 mg/kg twice daily orally and ivermectin 600 μg/kg once daily orally for 13 weeks of period. Nevertheless, no clinical improvement was observed and finally the dog was given up by the owner and donated to our clinic.

We decided to try the off-label use of selamectin instead of ivermectin orally given for the case. Selamectin was to be applied to the dog at 30 mg/kg topically once a day with oral cephalexin administration until the complete elimination of the mites would be achieved. The deep skin scrapings were to be performed weekly basis. However, the selamectin trial was ceased in two weeks because the skin lesions were too serious to be waited for the remission. The pruritus caused by secondary pyoderma existed consistently, which hastened formation of self-trauma. In addition, the number of mites observed from multiple skin scrapings were not decreased at all after the two weeks of therapy. By the end of the two weeks of spot-on selamectin therapy, the dog started to show diarrhea. The diarrhea was very severe and such condition went on for more than one month. Therefore the systemic antibiotic therapy had to be stopped regarding its concern about the disturbance of normal gut flora.

Finally we decided to try another off-label use option, which was weekly basis amitraz dip at higher concentration, 1000 ppm. As an antibacterial topical agent, 4% chlorhexidine solution was chosen twice a week basis rather than benzoyl peroxide concerned about the exacerbation of pruritus. No systemic antibiotics could be used since the diarrhea was not resolved yet. The number of mites and staphylococci were reevaluated at the beginning of therapy to be compared to the results obtained during the therapy every two weeks.

The dog was clipped on regularly basis as needed and taken bath with chlorhexidine prior to amitraz dip. Surprisingly, most of the pustules were gone with pruritus after two weeks of therapy and a remarkable decrease in the number of mites was observed although the skin was still erythematous. The systemic antibiotic therapy was to be adapted as soon as the diarrhea would disappear but the effect of chlorhexidine bath alone was good enough to get rid of the bacterial infection. No adverse effect associated with amitraz was seen throughout the therapy and the dog was very bright, alert and responsive all the time. After 9 weeks of therapy, the skin condition returned to the clinical normalcy and no detectable mite was seen from skin scrapings. The therapy was continued for 4 more weeks from the time when the negative skin scrapings were obtained to prevent relapse. The dog is clinically normal and being monitored for development of any abnormal dermatological signs for the time being.

Discussion

Ivermectin, a member of the avermectin family of compounds, was first introduced as an antiparasitic drug in 1981[31]. In dogs, ivermectin is approved only for the prevention of heartworm disease. Nevertheless, ivermectin is used in an extra-label manner to treat dogs with sarcoptic mange, cheyletiellosis, and other parasitic skin diseases. Ivermectin has been used successfully to treat canine generalized demodicosis when given 300-600 mg/kg orally once a day[6,18,21,23,26]. The cure rate was usually dose dependent and ivermectin was found effective in up to 83.3% of dogs with generalized demodicosis[23].

The therapeutic potential of the 0.5% alcohol base, pour on formulation of ivermectin (Ivomec pour-on® for cattle) in the treatment of chronic CGD has been evaluated because of its presumed longer residual effect when compared to the orally administered ivermectin in dogs[18]. Pour-on ivermectin was applied topically along the dorsal midline at 1500 mcg/kg three times per week for up to 6 months. While all dogs had a substantial reduction in the severity of clinical signs and in the number of *Demodex canis* mites found on skin scrapings, only one of 12 (7%) dogs was cured. The treatment efficacy of the topical formulation may have been negatively affected by the fact that only 7 of 12 dogs completed the 6 month trial. All the 12 dogs had a substantial reduction of clinical signs and numbers of *D. canis* mites on skin scrapings after 1-2 months of treatment though the overall success rate was low.

Selamectin is a recently introduced avermectin and is active against fleas (*Ctenocephalides*), ear mites (*Toadeaters*), sarcoptic mange (*Sarcoptes scabie*) and ticks in dogs and cats[3,30]. It is a member of avermectins with ivermectin, abamectin, eprinomectin and doramectin, which is one group of systemic macrocyclic lactones (SML) and have dual activity against endoparasites (antihelmintic) and ectoparasites (acaricide and insecticide) so called endectocide[30]. The mode of action of the SML has been studied but has still not been completely elucidated.

Although there is few study has been performed to investigate the efficacy of selamectin against *D. canis*, there has been a report about the efficacy of selamectin in the treatment of feline demodicosis[1]. Topical selamectin was applied to the cats infested with either *D. gatoi* or *D. cati* and it turned out that selamectin was ineffective when used for 6 weeks at eliminating infection with *Demodex spp.* Although it was ineffective for the complete elimination of mites, it was shown to cause the clinical improvement in 14 out of 17 cats. It was thought that the selamectin might be effective for the treatment of CGD due to its similar mode of action to that of ivermectin[3,30] so it was tried in this case evaluate the efficacy of spot-on selamectin application against *D. canis*. However, the two weeks of spot-on selamectin therapy on a daily basis at 5 times recommended dose didnt show any efficacy against *D. canis* in this case. The poor result obtained may be due to the short duration of therapy, which was only 2 weeks in this study or the inappropriate route of administration of selamectin. Two weeks of duration of spot-on selamectin therapy was too short to expect any improvement and it might had been possible to get the better result if we have extended the duration of therapy. In addition, the alteration of the route of administration, for example, orally like the way ivermectin is given for demodicosis might have induced better result. The pharmacokinetics of various routes of administration of selamectin in dogs has been reported[24]. The mean plasma concentration of selamectin in dogs after single oral doses at

24 mg/kg was kept higher than single topical doses within approximately 250 hours after administration. It is suspected that the reason why oral ivermectin administration is more effective than topical pour-on therapy may lie on such pharmacokinetics similar to that of selamectin. Other factors which might have attributed in the poor result could be the inadequate dose being too low and the degree of mite infestation by too many numbers of mites. Due to its higher safety margin in dogs than ivermectin[3], it is considered to be worthwhile to investigate the efficacy of selamectin against canine demodicosis.

Amitraz is an acaricide-insecticide from the formamidine family[30]. It was approved in the United States in 1982 for use as a topical dip for treating canine generalized demodicosis. It still remains the only product licensed for this condition. It is marketed in the United States and Canada as Mitaban (Upjohn, distributed by Janssen-Animal Health, Ontario, Canada), a 19.9% amitraz liquid concentrate that is applied as a 250-ppm amitraz solution to the dogs entire body every 2 weeks.

Its pharmacological activities include monoamine oxidase inhibition, α_2-aderenergic agonist activity and prostaglandin synthesis inhibition. The most common side effects attributed to amitraz treatment in dogs, which can be seen in about 30% of the patients for 12 to 36 hours post-treatment, are sommolence, lethargy, anorexia, pruritus and hypothermia[25,27]. Severe reactions or intoxications can be reversed with α_2-agonist inhibitors such as yohimbine or atipamezole[8].

The literature reports cure rates of amitraz ranging from 0 to 99%[4,5,9,13,15,25,26]. This vast discrepancy or reported efficacy is probably related to the different treatment protocols such as case selection, different concentrations of amitraz solution, frequency of application and different criteria for cured cases, including long-term follow-up periods[20]. In the actual long-term cure rate following, biweekly amitraz treatments with a one year follow-up interval are probably in the range of 60% to 80% for the typical population of dogs with CGD under 1.5 years of age[20].

In an attempt to increase the clinical efficacy of amitraz, unlicensed protocols have been developed involving more concentrated solutions of the drug applied more frequently. One study reported that improved success rates were achieved by doubling the frequency of treatment to once weekly[9]. In Europe, weekly applications of amitraz at concentrations of 500 to 1000 ppm were reported to be effective and safe in the treatment of CGD[4,12].

In present case study, the 1000 ppm amitraz solution was adapted and the result was satisfactory. The dog returned to the clinical normalcy in 9 weeks of therapy. None of the adverse effects associated with amitraz was observed in present case study. The efficacy of 1250 ppm amitraz solution applied to half body daily in CGD cases previously refractory to biweekly or weekly amitraz treatments has been evaluated[13]. A cure rate of 73% was obtained following the mean treatment duration of 10 weeks (ranged from 1 to 5 months). Although the high cure rate obtained from daily administration protocol, there are several disadvantages in its utilization in dogs with GD. Daily basis topical treatment is time consuming, potentially hazardous for both the dog and the patient compared to weekly basis treatment and not very cost-effective[25].

In the aspects of safety, cost and owners compliance, the 1000 ppm amitraz dip on weekly basis seems to be superior to the daily basis 1250 ppm dip as shown in this case study.

As an antibacterial topical, 4% chlorhexidine solution was chosen rather than benzoyl peroxide concerned about its potential to exacerbate the pruritus. It showed a great efficacy and most of the pustules and pruritus were disappeared after 4 treatments. It should be noted that the antibacterial topical agent alone yielded the cure of superficial pyoderma in this case. The treatment of pyoderma is usually known to require the concurrent systemic antibiotics with topicals but it may not in some cases. The skin condition of the dog in this case was as bad as usual dogs with superficial pyoderma secondary to CGD, and seemed to require systemic antibiotics for the cure. However, the oral antibiotics had to be withdrawn because the dog had consistent diarrhea, which was considered to be caused by disturbance of normal gut flora following the previous long-term use of cephalexin[11,22]. The GI sign could be thought to be resulted from the high dose of selamectin. However, the dog was perfectly normal other than diarrhea and the adverse effects of selamectin other than dermatologic sign are extremely rare. Moreover, they are not likely to develop at 5 times recommended dose when administered topically. The clinical study on the efficacy of topical antibacterial agent alone in superficial pyoderma secondary to CGD is worthwhile to be performed in a large scale.

Conclusion

A remarkable remission was obtained in 9 weeks of 0.1% weekly basis amitraz therapy with 4% chlorhexidine bath given twice a week in this case 1 year old, intact female Japanese Chin dog weighing 3.1 kg with juvenile onset demodicosis. In addition no adverse effect associated with amitraz was observed. Therefore, the weekly basis 0.1% amitraz therapy with topical chlorhexidine bath might be considered to be superior to the other therapies tried herein in aspects of efficacy, safety and cost.

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Japanese Chin 종에서 발생한 Ivermectin에 반응을 보이지 않은 전신성 농성 모낭충 감염증에 대한 0.1% Amitraz와 4% Chlorhexidine의 국소치료 일례

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요 약: 중성화 수술을 받지 않은 3.1 kg의 1년령 암컷 일본 찡견이 자견발생모낭충증의 전형적인 증상으로 경북대학교 수의과대학 부속동물병원에 내원하였다. 일반적인 신체검사, 피부박리검사, 혈액화학 검사, 내분비검사와 세균배양검사 등을 실시하였다. 내원 당시 피부 병변을 제외한 환축의 상태는 양호하였으며, 혈액화학치, T_3, T_4, fT_4는 모두 정상이었다. 그러나, 피부박리검사에서 다수의 모낭충이 관찰되었고, 농포를 이용한 세균배양 결과 구균이 검출되어 속발성 표재성농피증을 동반한 자견발생모낭충증으로 확진하였다. 치료를 위하여 13주간 매일 1회 600 μg/kg의 ivermectin을 매일 2회 25 mg/kg의 cephalexin과 함께 투여하였으나 임상증상이 호전되지 않았으므로 일주일 간격으로 30 mg/kg의 selamectin을 cephalexin과 함께 국소 투여하는 방법을 실험적으로 2주간 실시하였다. 그러나, 임상증상이 오히려 더 악화되어 주 1회 0.1% amitraz dip을 주 2회 4% chlorhexidine 샴푸와 함께 실시하였다. 그 결과, 환축은 급속도로 호전되어 속발성 농피증에 의한 피부병변과 이에 동반된 소양증은 치료 실시 후 2주 경에 거의 사라졌으며 9주 경에는 피부박리검사에서 모낭충이 검출되지 않았을 뿐만 아니라 환축의 피모도 거의 정상으로 회복되었다. 재발을 막기 위하여 피부박리검사에서 음성 결과를 얻은 후에도 4 주간 더 치료하였다. 현재 환축은 임상적으로 정상이며, 모낭충증의 재발여부를 관찰 중에 있다.

주요어 : generalized demodicosis, amitraz, ivermectin, selamectin, dog