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Buparvaquone

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Abstract: Theileriosis is a type of blood protozoan infection caused by the transmission of *Theileria* spp. species in tropical and subtropical regions by ticks belonging to the *Ixodidae* family. The disease progresses with high mortality and morbidity especially in ruminants. While deaths are observed in the first few days in peracute cases, it is reported that deaths are observed within the first weeks in acute cases. Fever, lymphadenopathy, respiratory distress, increase in heart rate, decrease in milk yield, weight loss, abortion and death are observed in patients. Buparvaquone, an antiprotozoal drug of the hydroxynaphthoquinone group, is the single most effective drug used in the treatment of the disease. Although it is recommended to use 2.5 mg/kg intramuscularly against Theileriosis infection in cattle, it can be used in the same dosage regimen 2-3 days later if deemed necessary by the physician. It is not recommended to use the drug together with vaccines, as local reactions may occur in the area where it is applied. The drug is generally considered safe. Since the disease is transmitted by ticks, it is recommended to add an ectoparasitic agent to the treatment protocol. In this review, it has been tried to give information about the use of buparvaquone in the treatment of Theileriosis.

Keywords: Buparvaquone, theileriosis, animal species

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Özet: Theileriosis tropikal ve subtropikal bölgelerde *Theileria* spp. türlerinin *Ixodidae* ailesi ait kenelerle nakledilmesi sonucu gelişen bir tür kan protozoonu enfeksiyonudur. Hastalık özellikle ruminantlarda yüksek mortalite ve morbitide ile seyretmektedir. Perakut vakalarda ilk birkaç gün içinde ölümler gözlenirken, akut vakalarda ilk haftalar içinde ölümler gözlendiği bildirilmektedir. Hastalarda ateş, lenfadenopati, solunum güçlüğü, kalp atım sayısında artış, süt veriminde azalma, canlı ağırlık kaybı, abort ve ölümler gözlenmektedir. Hidroksinaftokinon grubu antiprotozoal ilaç olan buparvakuon hastalığın tedavisinde kullanılan en etkili tek ilaçtır. Sığırlarda, Theileriosis enfeksiyonuna karşı ilacın 2.5 mg/kg dozunda kas içi kullanımı önerilmekle birlikte hekim tarafından gerekli görüldüğü durumda ise 2-3 gün sonra aynı dozaj rejiminde kullanılabilir. Uygulandığı bölgede lokal reaksiyonlar oluşabileceğinden ilacın aşılarla birlikte kullanılması önerilmemektedir. İlaç genel anlamda güvenli kabul edilmektedir. Hastalığın kenelerle nakil edilmesi nedeni ile tedavi protokolüne bir ektoparaziter ajan eklenmesi tavsiye edilmektedir. Bu derlemede Theileriosis tedavisinde buparvakuon kullanımı hakkında bilgiler verilmeye çalışılmıştır.

Anahtar Kelimeler: Buparvakuon, theileriosis, hayvan türleri

1.Introduction

Buparvaquone is a hydroxynaphthoquinone group antiprotozoal drug. The drug is licensed for use at a dose of 2.5 mg/kg (Intramuscular (IM), a second application may be given 2-3 days later if necessary) in the treatment of Theileriosis in cattle (1, 2, 3). It is believed that the drug exerts its effects by inhibiting the respiratory system activities of parasites (4). The infection is associated with high morbidity and mortality, especially in cultured breed cattle. The causative agent is transmitted through ticks belonging to the *Ixodidae* family to ruminants (cattle, sheep, goats, buffalo), and equids (5). It is stated that it is detected in milk 35 days after the drug is applied (6). Local reactions can occur at the site of drug administration. The drug should be administered at a single application site in a maximum volume of 10 milliliters (mL). Additionally, its use in conjunction with vaccines is not recommended (1). In cases where the benefit-risk balance is considered in pregnant cattle, a decrease in the drug's effectiveness has been reported (7). In a study investigating the safety of the drug in sheep, it was indicated that there were no changes in hematological parameters, no effects on malondialdehyde, total antioxidant status, catalase, glutathione peroxidase, superoxide dismutase, creatine kinase-MB, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, total protein, albumin, globulin, and creatinine levels. However, troponin I and blood urea nitrogen levels increased, and fluctuations in alkaline phosphatase levels were observed. The drug was generally

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considered safe (8). In a study assessing its reliability in sheep, the combined use of antiprotozoals (imidocarb + buparvaquone + oxytetracycline) did not induce oxidative stress, cardiotoxicity and nephrotoxicity (9). In the treatment of the disease, ectoparasitic application should also be considered for tick control. However, the development of resistance to drugs used against certain ticks has been observed. Resistance to buparvaquone, the sole option for the treatment of Theileriosis today, has been identified. This resistance is attributed to mutations in the cytochrome b (cyto b) gene. This situation further exacerbates the severity of the disease (10). In a study involving *T. annulata*, it has been suggested that buparvaquone's failure in treatment may be due to one or multiple mutations in the cyto b gene (11).

2. Usage of buparvaquone

Theileriosis develops as a result of the transmission of *Theileria* spp. species by ticks in tropical and mediterranean regions. Specifically, the main agent for ruminants is noted to be the *T. annulata* species. In the parasitic cycle, it is stated that the agent infects erythrocytes most recently and clinical signs are observed approximately 10-25 days after the agent is transmitted by ticks (12). It is reported that in infection, decrease in hemoglobin, hematocrit and erythrocyte count (13), oxidative stress (14), fever, lymphadenopathy, respiratory distress, increase in heart rate, decrease in milk yield, live weight loss, abortion and deaths are observed. In peracute cases, death occurs within 3-5 days, while in acute cases, deaths are reported within 1-2 weeks. The use of buparvaquone, which is used in the treatment of the disease, is said to reduce deaths by up to 10% (12). When the disease is treated early in cattle, treatment success increases (15). The recommended single dose has also been shown to be effective (16). Supportive treatments for anemia and secondary infections have been suggested to enhance treatment efficacy (17). In natural infections with *Theileria* spp. in different ages of cattle, the use of buparvaquone in conjunction with oxytetracycline has been reported to achieve a treatment rate of over 90% (18). Another study found it to be effective at a rate of 95.2% (19). Successful treatment of Theileriosis in cattle and calves has been reported using buparvaquone, meloxicam, vitamins (A, E, D3, Biotin), and flumethrin applications (20). It has been reported that buparvaquone and oxytetracycline treatment was effective in cattle infected with *Theileria orientalis*, but complete elimination was not achieved (21). It was stated that a one-month-old Kankrej breed cattle calf did not suckle milk, was stagnant, and had fever, and Theileriosis was diagnosed by blood examination. In the treatment, it has been stated that buparvaquone is not used in severely anemic animals because it may cause sudden death, and treatment is performed with dexamethasone, oxytetracycline and blood transfusion (22). It has been reported that the treatment of a 3-month-old calf infected with *Theileria orientalis* was started with parenteral buparvaquone, vitamins (A, E, D3) and calcium borogluconate, and 2 days later, oxytetracycline, metoclopramide and liquid-electrolyte therapy were administered and the patient recovered (23). It has been stated that buparvaquone, meloxicam, nandrolone and vitamin applications were used in the treatment of Theileriosis calves with bilateral exophthalmos (24). In another case report, it was stated that exophthalmos was observed in a calf with Theileriosis, and in the treatment, oxytetracycline, meloxicam, chlorpheniramine, multivitamin and deltemethrin were applied in addition to buparvaquone application every 2 days (25).

The presence of Theileriosis infection has also been observed in other animal species, and the use of buparvaquone for treatment has been suggested. Theileriosis in buffalo can lead to high rates of mortality if left untreated, and it is noted that drugs used in cattle can also be used in buffalo (26). A study in buffalo reported that adults are more heavily infected than youngs, and blood parameters become abnormal. Buparvaquone application was found to be highly effective in treatment (27). Early buparvaquone treatment was found to be highly effective in infected buffalo, while its efficacy decreased when administered in later stages of the disease (28). Theileriosis has also been reported in sheep, causing significant economic losses. In naturally infected sheep, buparvaquone was found to be around 90% effective in comparison to oxytetracycline, which was effective at around 30% (29). It has been suggested that buparvaquone could partially affect *Theileria equi* infections in horses (30). In a case report, it was stated that a 10-year-old horse with T. equi infected Theileriosis had colic, stagnation, anorexia, runny nose, dark yellow urine, fever, increased pulse rate, icteric conjunctiva, anemia, leukopenia, thrombocytopenia. It has been reported that the horse recovered with buparvaquone (2.5 mg/kg, IM) as well as supportive treatment (31). Theileriosis has been reported in antelope (32) and deer (33), and the use of buparvaquone for treatment has been suggested.

Studies have also examined the effectiveness of buparvaquone against different parasites. In dogs infected with Babesia vulpes, it has been suggested that buparvaquone (5 mg/kg, IM, 2 doses with a 2-day interval) in combination with azithromycin (10 mg/kg, oral, once a day, 10 days) could be partially effective (30). In a study, infection caused by *Haemoproteus columbae* was detected in a pigeon. It was stated that anorexia, depression and torticollis were observed in the pigeon and multivitamin and deltamethrin were applied in addition to buparvaquone in the treatment (34). In vitro studies have shown that buparvaquone is effective against Leishmania pathogens. However, its low solubility limits its effectiveness in vivo. Different formulations have been developed to overcome this limitation. Research using lipid carriers has indicated similar effects to miltefosine (35). It has

been suggested that buparvaquone could be an alternative option for treating fungal infections caused by *Sporothrix brasiliensis* in cats (36).

3. Conclusion

Theileriosis is a blood protozoan infection transmitted by ticks and can lead to significant mortality rates, especially in ruminants, if left untreated.

Currently, buparvaquone remains the first and most important option for treatment, maintaining its significance.

The drug should be administered as early as possible. In cases of necessity, a second application should be considered 2-3 days later.

Providing supportive treatment with oxytetracycline, nonsteroidal anti-inflammatory drugs, vitamins (A, E, D3, Biotin), and fluid support can enhance the success rate of treatment.

Alongside Theileriosis treatment, ectoparasitic treatment must also be administered.

However, the emergence of buparvaquone resistance observed in recent years among pathogens could lead to serious problems in the future.

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