Babesia rodhaini感染マウスに対するdiminazene diaceurateの効力における日内変動

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Daily Efficacy Variation of Diminazene Diaceturate in Mice Infected with *Babesia rodhaini*

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Circadian efficacy rhythms of drugs on the market have been extensively demonstrated by experiments with animals [2, 7]. The rhythms greatly influence the therapeutic effects by both reduction in toxicity of drugs and enhancement of their efficacy. In clinical medicine, chronotherapy has been practically applied to steroids and anti-cancer drugs to decrease their toxicity and to enhance their efficacy [1, 4, 5]. However, no studies have been made on the chronotherapy with anti-piroplasma drugs. This study was designed to evaluate the effects of chronotherapy with diminazene diaceturate against *Babesia rodhaini*-infected mice.

Four-week-old female ICR mice (Clea Japan Inc.) were used in the experiments. From at least 1 week before experiments to their end, all mice were kept at a room temperature of 22±2°C, on a 12-hour alternating light-dark cycle of light from 09:00 to 21:00. The animals were fed on solid feed and tap water *ad libitum*. The pathogenic agent used in this study was an Australian *B. rodhaini* strain. As inoculated controls 120 mice were randamly divided into 6 groups of 20 animals each. The 6 groups of mice were intraperitoneally inoculated with 2×10^7 parasitized RBC at 12:00, 16:00, 20:00, 00:00, 04:00 and 08:00 respectively. 72 hours after inoculation, blood was collected from all the mice in the tail vein and the blood smears were stained by Giemsa method. The parasitized RBC percentages were calculated in the 6 groups of mice from the number of parasitized RBC in 1000 RBC and were analysed by Student's t-test after transformed by the inverse sine method. 254 mice were randomly divided into 6 infected- and -treated groups, 5 of which consisted of 43 animals each and 1 of 39 animals. All the animals were intraperitoneally inoculated with parasites by the same procedures as used in the inoculated controls. 72 hours after inoculation, a single dose of 9.5 mg/kg diminazene diaceturate was subcutaneously administered to the 6 groups of mice at 12:00, 16:00, 20:00, 00:00, 04:00 and 08:00 respectively. The efficacy of the drug was evaluated by the survival rates of mice on day 7 after administration and was analysed by Chi-square test.

The mean parasitized RBC percentages at 72 hours after inoculation were 23.8% in mice inoculated at 00:00, 27.1% at 04:00, 26.1% at 08:00, 28.0% at 12:00, 22.9% at 16:00 and 29.2% at 20:00 and were not statistically different between the 6 groups. Although all the non-treated mice died by day 8 after inoculation, the survival rates of treated mice on day 7 after administration varied according to drug administration time: the rate was the highest (67.4%) in the group medicated at 12:00, whereas it was the lowest (16.3%) in that at 4:00 (Fig. 1). The differences in survival rates were statistically significant between the group treated at 4:00 and the other 5 groups, and also between the group treated at 12:00 and those at 4:00, 8:00 and 16:00.

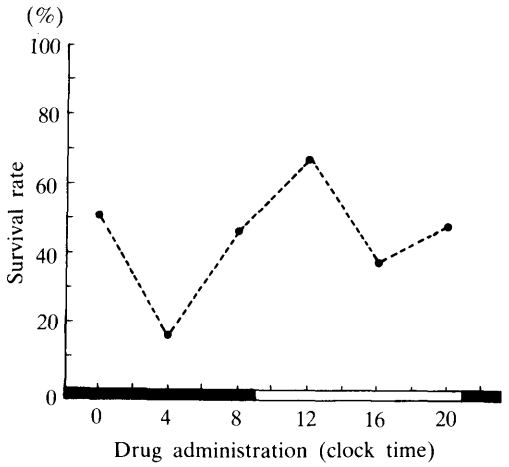

Fig. 1. Survival rates of *B. rodhaini*-infected mice treated with diminazene diaceturate at different clock times, at each administration time 43 mice were treated except at 16:00 when 39 mice were used. Black region: dark phase, white region: light phase.

All the surviving mice recovered from the infection.

Cardosa, *et al.* suggested that therapeutic responses will be enhanced by utilizing fluctuations of host resistance to the drug because the efficacy of cyclophosphamide against leukemic (L1210) mice is influenced by administration time [3]. Considering these results, the suvival rates in the present experiments will be hardly influenced by the toxicity of the drug nor by the degree of parasitemia at administration, because the parasitized RBC parcentages were not different between the 6 groups at administration (72 hours after inoculation) and the drug was not toxic to mice in the dose administered [6]. Therefore, the efficacy of diminazene diaceturate against *B. rodhaini*-infected mice is considered to be clearly influenced by administration time.

In conclusion, diminazene diaceturate was more efficacious against *B. rodhaini*-infected mice when administered at the light phase than at the dark phase.

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要　約

Babesia rodhaini 感染マウスに対する diminazene diaceturate の効力における日内変動（短報）：須永藤子・並河和彦・菅野康則（麻布大学獣医学部伝染病学講座）——*Babesia rodhaini* 感染マウスに対して感染72時間後の0時，4時，8時，（以上暗期），12時，16時，20時（以上明期）に diminazene diaceturate 9.5 mg/kg を1回投与すると，投与後7日目の生存率は明期投与群に高く，暗期投与群に低くなる傾向が認められ，特に，明期の12時投与群の生存率は67.4%であったのに対し，暗期の4時投与群は16.3%で，両者間に有意の差が認められた．