EXPERIMENTAL BIOLOGY

Effect of Diaminodiphenyl Sulfone on Circadian Rhythms of Hematological Parameters in Mice

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The study explores the effect of diaminodiphenyl sulfone administered at different times of the day in fall and spring on the diurnal rhythms of hemoglobin level and erythrocyte and leukocyte counts in CBA mice. Changes in the rhythmic patterns of these parameters depend on the season and the time of treatment.

Key Words: *biological rhythms; hematological parameters; diaminodiphenyl sulfone*

There are two ways of improving the treatment of lepra: creation of novel antilepra drugs and optimization of the use of existing preparations. Chronopharmacological approach is now gaining wide acceptance in antibacterial therapy. Administration of various drugs with respect to the time elevates their therapeutic index and reduces their toxicity. The therapeutic effect of a preparation administered at different times can be the same, whereas its therapeutic index can be substantially decreased due to chronotoxicity. Moreover, the disease also affects the rhythm of physiological processes. An additional influence may aggravate desynchronosis and disturb adaptation [1,4-8]. This influence may be especially pronounced in chronic diseases such as lepra and tuberculosis that require long-term complex therapy [3,9]. The main antilepra drug DDS (4,4'-diaminodiphenyl sulfone, dapsone) possesses antioxidant and immunostimulating activities and is successfully used in the treatment of some diseases, tuberculosis in particular.

The aim of the present study was to evaluate the effect of DDS on the rhythmostasis of some hematological parameters.

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MATERIALS AND METHODS

Experiments were carried out in fall and spring on 320 CBA mice of both sexes synchronized by the age, weight, maintenance conditions, and nutrition. In each season, the experiment consisted of 2 series (80 animals per series). In each series, the animals were divided into control and experimental groups. Experimental mice received DDS in a dose of 25 mg/kg intragastrally at either 9:00 (morning series) or 17:00 (evening series). Each experimental point comprised 5-8 animals. The controls received no preparation. The mice were sacrificed every 4 h over 36 h, and the blood was sampled. Hemoglobin (Hb) was measured by the hemoglobin-cyanide method, and erythrocytes and leukocytes were routinely counted [2]. The data were processed using the Student' *t* test. Chronograms of the first day of the experiment were analyzed.

RESULTS

It was found that DDS affects rhythmostasis of Hb, erythrocytes, and leukocytes. This effect is variously pronounced in different seasons and depends on the time of administration.

As seen from Fig. 1, *a*, in the day series the chronogram of Hb in control mice represents a half-

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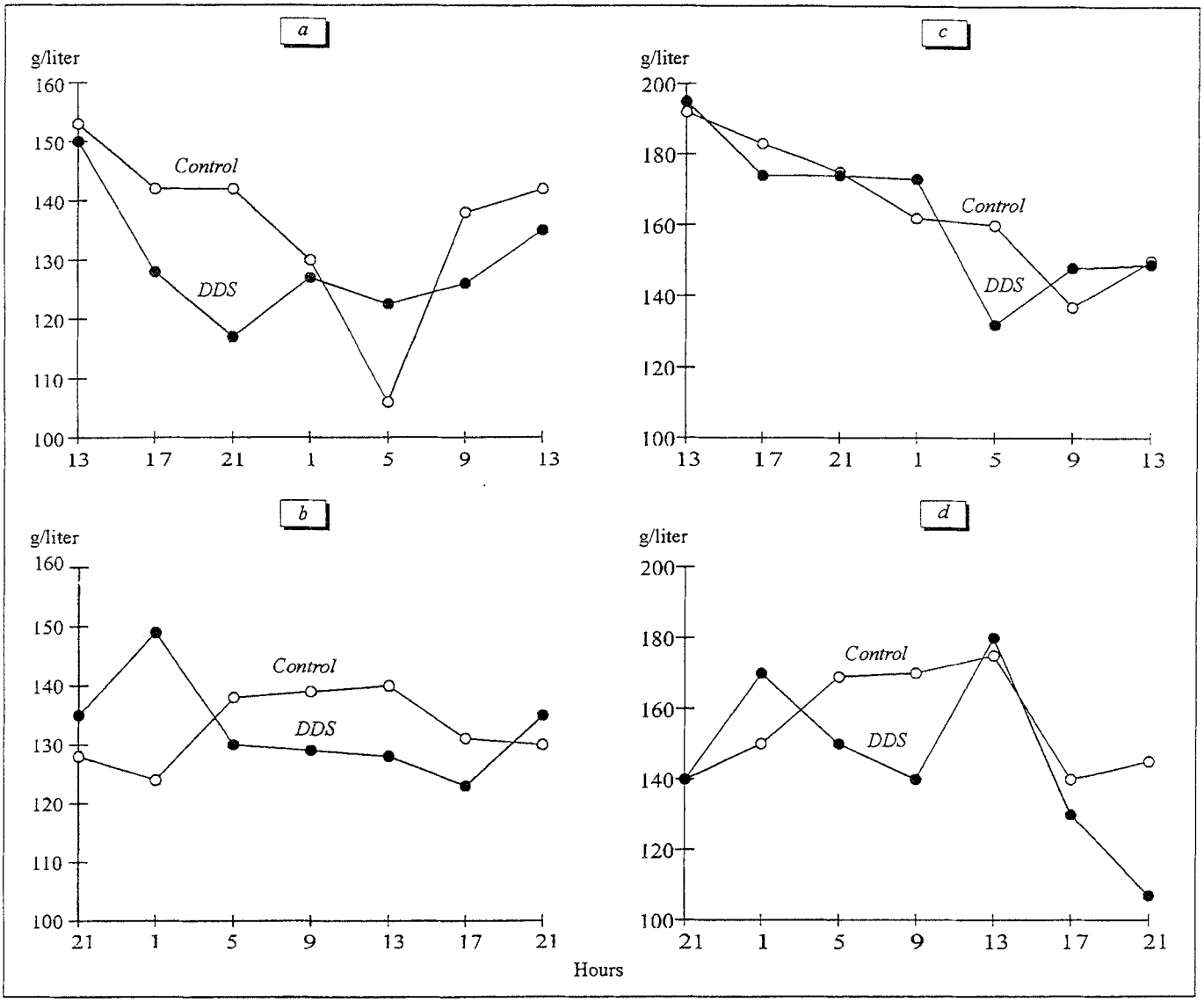

Fig. 1. Dynamics of hemoglobin level in DDS-treated mice. Here and in Figs. 2 and 3: fall: morning (*a*) and evening (*b*) administration; spring: morning (*c*) and evening (*d*) administration.

wave with the maximum at 13:00 and the minimum at 5:00. Analogous phasic changes in the Hb level with the maximum at 9:00 and the minimum at 1:00 h are observed in the evening control group. In mice given DDS at 9:00, the rhythmic pattern of blood Hb level was preserved, the mesor of Hb and the absolute amplitude of fluctuations being slightly lower than in the control. The acrophase remained unaffected, while the minimum was shifted 8 to the left in comparison with the control mice (to 21:00). On the next day at 13:00 the level of Hb surpassed the mesor and significantly differed from the minimum.

When the drug was administered at 17:00, a rise of the level of Hb was noted 4 h later. This parameter attained the maximum at 1:00 and than dropped to the minimum at 17:00. On the whole, such a dynamics is characteristic of the rhythm inversion (Fig. 1, *b*). The mesor did not differ from the control, the absolute amplitude was slightly increased, whereas the relative amplitude was 2.6-fold lower than in nontreated controls. Rhythmic fluctuations of the Hb level were also observed in spring. The acrophase was recorded at 13:00 h; the minimum in the morning and evening groups was noted at 9:00 and 21:00, respectively (Fig. 1, *c*, *d*). In mice given DDS at 9:00, the pattern and the parameters of Hb fluctuations did not differ from that in the control group. The minimum was shifted from 9:00 to 5:00 h. Administration of DDS at 17:00 substantially affected the parameters on Hb rhythm: two maxima of Hb were noted and the amplitude of fluctuations 2-fold surpassed that in the control group. The relative amplitude to the end of the experiment was lower by 50%

than in the nontreated controls. The mesor was decreased in both schemes of administration.

Figure 2 presents chronograms of the erythrocyte count. In fall, rhythmic fluctuations of this parameter were observed in both the morning and evening groups. The number of erythrocytes had two maxima: at 13:00 and 21:00, while the minimum was noted at 5:00 (morning group) and at 1:00 (evening group). When DDS was administered at 9:00, a phasic shift occurred: the first maximum shifted from 21:00 to 13:00, the second shifted from 13:00 to 5:00, while the minimum was noted at 1:00. The mesor remained unchanged; the absolute amplitude increased 2-fold, while the relative amplitude was 70% lower than in the control (Fig. 2, *a*). When DDS was administered at 17:00, the minimum shifted from 1:00 to 5:00, and the absolute and relative amplitudes decreased by 40 and 50%, respectively. The mesor did not differ statistically from the control (Fig. 2, *b*). In spring, the number of erythrocytes 4 h after morning administration was significantly higher than in the controls. This parameter dropped to 17:00, and then the rhythmic pattern of fluctuations was not restored. The mesor remained unchanged. After evening administration, we observed an earlier onset of the phase when the number of erythrocytes surpassed the mesor; other parameters of the harmonics were more stable.

Figure 3, *a* and *b* presents the chronograms of leukocyte count in fall. In the morning and evening groups, the acrophases were noted at 1:00 and the minimum at 13:00 and 17:00, respectively. In animals given DDS at 9:00 h, the absolute amplitude of fluctuations was slightly increased, while in evening administrations the chronogram of leukocyte count coincided with the control. In spring, we observed

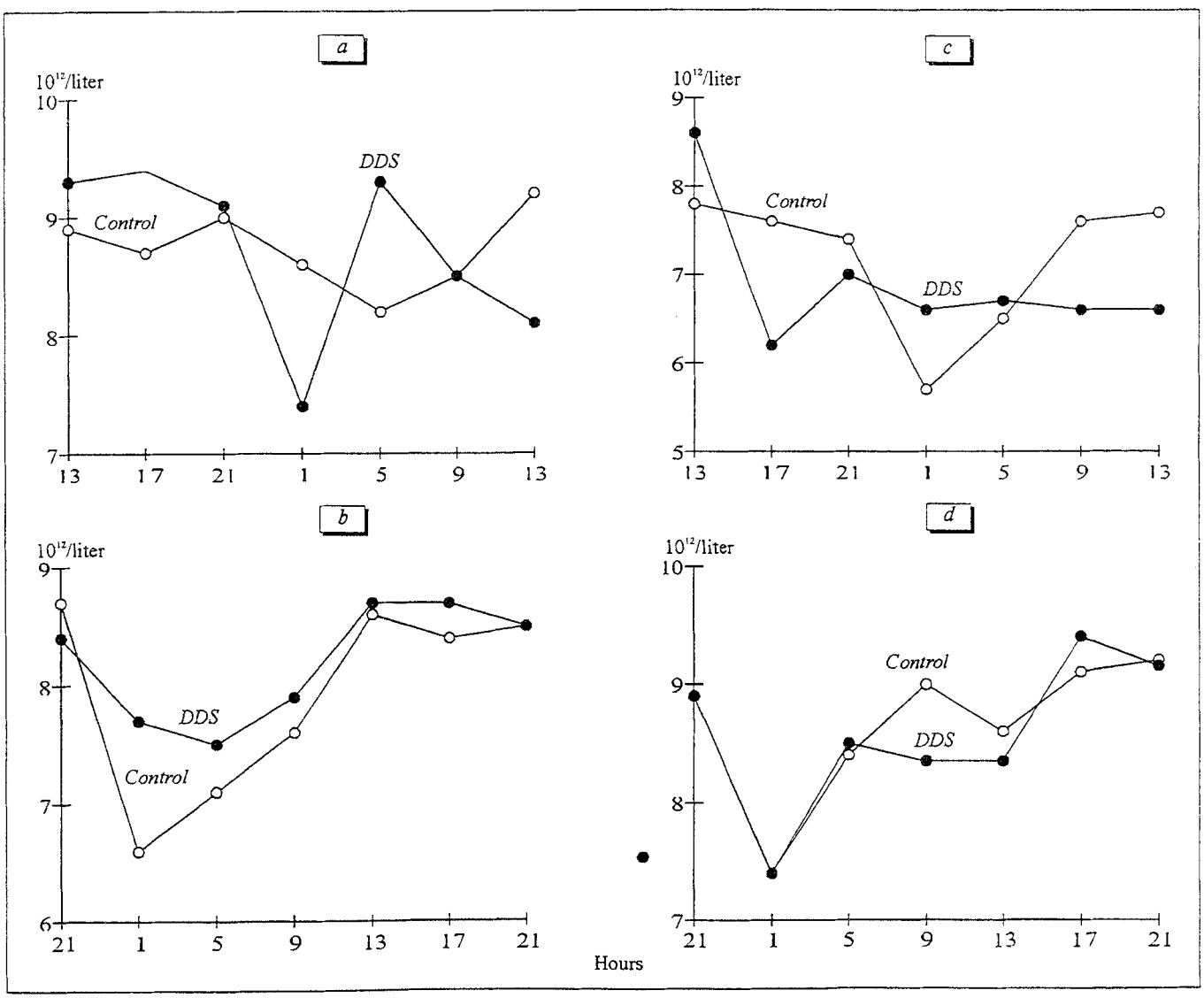

Fig. 2. Dynamics of blood erythrocyte count in DDS-treated mice.

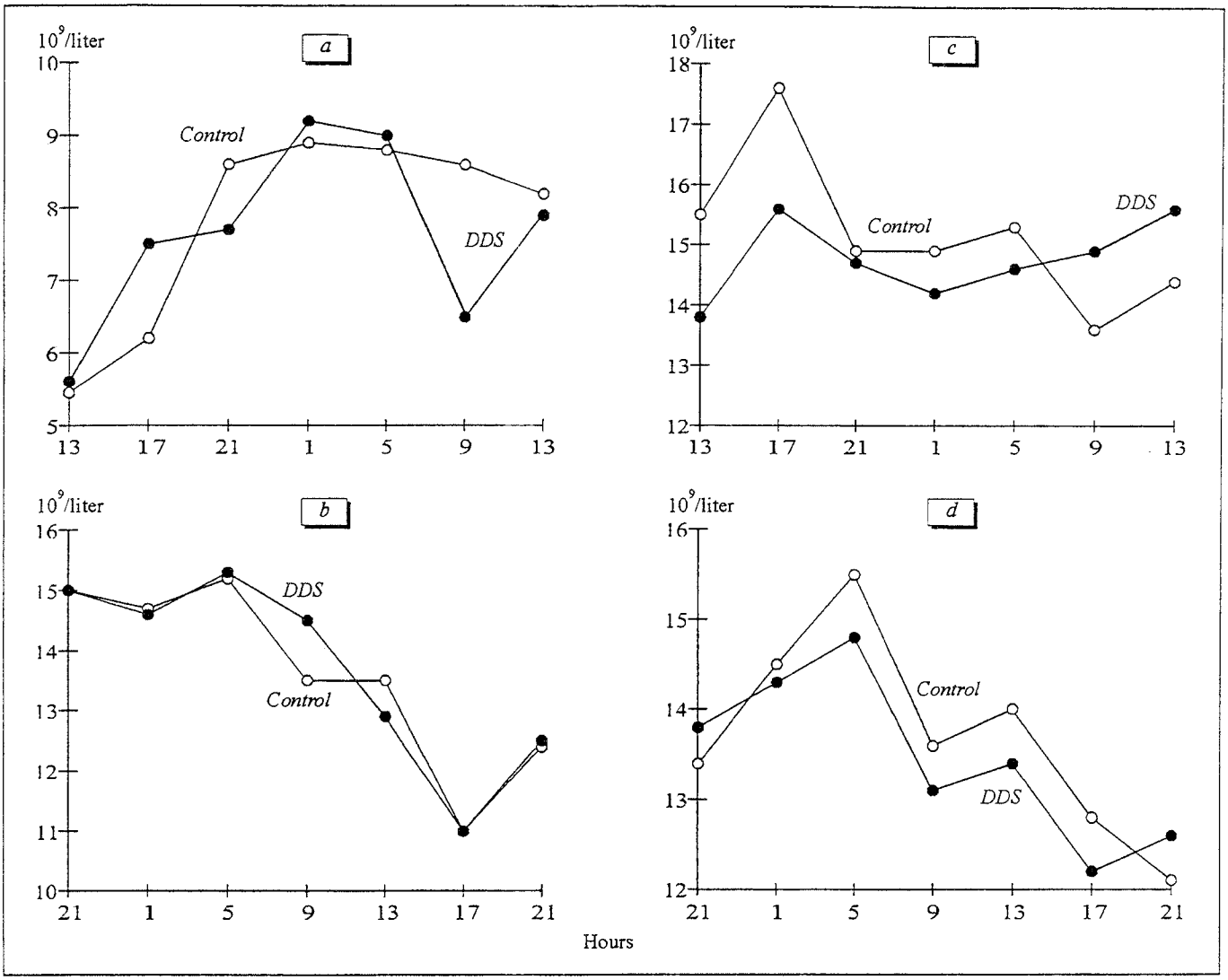

Fig. 3. Dynamics of blood leukocyte count in DDS-treated mice.

clear-cut rhythmic fluctuations of the leukocyte count with the maximum at 17:00 and 1:00 and the minimum at 9:00 and 21:00 in the morning and evening groups, respectively. In mice given DDS at 9:00, the maximum shifted from 9:00 to 1:00; the absolute amplitude decreased 2-fold; the mesor was slightly lower than in the control group. In the evening group, the chronogram of leukocyte count coincided with the control curve. The negative effect of the drug manifested itself in a 1.5-fold decrease of the absolute amplitude of fluctuations.

Thus, Hb and erythrocytes were more sensitive to DDS both in fall and spring. Nevertheless, it can be noted that in fall morning administration of the drug is preferable. In spring, it seems difficult to recommend the time of DDS administration, since pronounced alteration of the rhythmostasis occurred both in the morning and evening groups. The observed desynchronization of the usually parallel changes in erythrocyte count and Hb level suggests that these changes should not be ignored. Therefore, in spring a more careful medical and laboratory control is required.

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