IMMUNODEPRESSIVE PROPERTIES OF PHENTYRINE

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The immunodepressive activity of phentyrine (o[p-di(2-chloroethyl)aminophenyl]D,L-tyrosine) was investigated. The compound was given to mice by mouth in a dose of 50 mg/kg. The results of these experiments showed that phentyrine has a marked immunodepressive action on transplantation immunity and on the production of plaque- and rosette-forming cells. The immunodepressive action of phentyrine is stronger than that of azathioprine under the same experimental conditions.

KEY WORDS: phentyrine; azathioprine; transplantation immunity; immunocompetent cells; immunodepression.

The problem of tissue incompatibility has compelled research workers to seek substances that would selectively destroy lymphocytes or would neutralize their immunologic powers but at the same time would spare the hematopoietic tissue. Immunodepressive properties have been found in many antitumor preparations [2, 5], such as cyclophosphamide and degranol. A common feature of these substances is the presence of a di(2-chloroethyl)amino group, which determines their alkylating ability, as a result of which they form the group of immunodepressants of alkylating type [4].

In the investigation described below the immunodepressive properties of o[p-di(2-chloroethyl)aminophenyl]D,L-tyrosine dihydrochloride, to which the name phentyrine has been given,* were studied.

EXPERIMENTAL METHOD

Phentyrine synthesized at the Lensovet Leningrad Technological Institute [1] and azathioprine obtained at the S. Ordzhonikidze Pharmaceutical All-Union Chemical Research Institute [3] were used.

The experimental animals were female CBA mice, male C57BL/6 mice, and female F_1(CBA × C57BL/6) hybrids.

The period of survival of the skin graft in mice distinguished by a strong histocompatibility locus was determined by the method of Billingham and Medawar [6]. Phentyrine was given by mouth to the female CBA mice in a dose of 50 mg/kg in starch mucilage daily for 10 days before grafting and on the 7th, 8th, 9th, and 10th days after grafting the skin from the tail of male C57BL/6 mice.

Antibody-forming cells (the method of Jerne and Nordin [7]) and rosette-forming cells (Revillard's [8] method) were determined in the same suspension of spleen cells, obtained on the 4th day after immunization of the mice with sheep's red cells. The following experimental scheme was used. Phentyrine was given daily for 10 days in a dose of 50 mg/kg by mouth. Before the beginning of the experiment and on the 6th, 11th, 20th, and 30th days after the beginning of administration of the preparation, the number of antibody- and rosette-forming cells was counted. To compare phentyrine with an existing immunodepressant

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TABLE 1. Effect of Phentyrine and Azathioprine on Immune Response

Test	Control	6th day		11th day		20-th day		30-th day	
		phentyrine	azathioprine	phentyrine	azathioprine	phentyrine	azathioprine	phentyrine	azathioprine
No. of antibody-forming cells ($\times 10^3$)	12,7 ± 0,21 (10)	2,35 ± 0,54 (10)	10,3 ± 1,19 (10)	0,28 ± 0,04 (9)	19,75 ± 0,96 (10)	0,23 ± 0,04 (9)	32,7 ± 4,95 (8)	5,9 ± 0,31 (7)	13,55 ± 0,84 (10)
No. of rosette-forming cells ($\times 10^6$)	1,19 ± 0,09 (10)	0,19 ± 0,03 (10)	0,8 ± 0,05 (10)	0,25 ± 0,005 (10)	1,49 ± 0,1 (10)	0,043 ± 0,005 (10)	1,37 ± 0,17 (8)	0,42 ± 0,03 (8)	1,82 ± 0,16 (10)

Legend. Number of animals investigated given in parentheses.

widely used in clinical practice, azathioprine was chosen and given by mouth in a dose of 50 mg/kg by the same scheme.

EXPERIMENTAL RESULTS

Phentyrine caused a statistically signficant prolongation of survival of the skin graft to 18.5 ± 0.7 days (14.1 ± 0.3 days in animals treated with azathiorpine and 11.5 ± 0.2 days in the control animals).

Phentyrine led to marked depression of the immune response during immunization by sheep's brain cells (Table 1). Not until 3 weeks after the end of the course of phentyrine was the reactivity of the animals restored to about 50% of its initial level. The inhibitory action of phentyrine when given in a comparatively small daily dose (less than 0.1 LD_{50}) continued, it will be noted, throughout the period of observation. Accordingly, the possibility of giving phentyrine in comparatively small doses is a very valuable property of this compound. Azathioprine, if used to inhibit immunogenesis in the same dose as phentyrine, proved to be ineffective. Furthermore, 10 days after the end of the course of treatment with the compound the number of antibody-forming cells was 3 times higher than initially, whereas the number of rosette-forming cells was close to the figure found in intact animals (Table 1).

Consequently, under the experimental conditions used, phentyrine had greater immunodepressive activity than azathioprine.

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