Efficiency of Interferon Inductor Anaferon (Pediatric Formulation) in Prophylaxis of Acute Respiratory Infections in Sickly Children

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Prophylactic efficiency and safety of anaferon (pediatric formulation) in children aging 1 month to 4 years, including sickly children, was proven. The use of the preparation in children reduced the incidence of acute respiratory infections, alleviated the course of the disease, and decreased the incidence of detection of viral antigens in nasal meatuses.

Key Words: *anaferon (pediatric formulation); sickly children; acute respiratory infections; viral antigen*

The term "sickly children" (SC) defines a group of children distinguished during regular medical check-ups and characterized by higher incidence (compared to age-matched children) of acute respiratory viral infections (ARVI) [3]. Repeated respiratory infections impair the functions of various systems and lead to further suppression of functional activity of all elements of the immunity, which in turn, provides conditions for acute respiratory diseases (ARD), thereby a vicious circle is formed. Frequent drug treatment (non-steroid anti-inflammatory drugs, antibiotics) leads to the development of immunosuppression. SC constitute 20-40% of children population.

IFN production, an important component of the competent immune response to viral infection, is impaired in SC [4].

In view of high morbidity of SC, especially in the presence of a wide spectrum of ARD-inducing agents, obligate nonspecific measures are required for these children in addition to widely accepted anti-influenza vaccination. The use of immunocorrectors, *e.g.* IFN and their inductors, is the most promising way. In the Department of Respiratory Viral Infections in Children, Institute of Influenza, Russian Academy of Medical Sciences, prophylactic efficiency of various preparations, including anaferon (pediatric formulation, AP) containing antibodies to IFN-γ in ultralow doses, was evaluated. AP did not suppress activity of IFN-γ, but even modifies it enhancing the production of this cytokine [2].

AP was registered at Ministry of Health Care (registration No. 000372/01, 31.05.2007) and was approved for commercial manufacturing and medical use.

MATERIALS AND METHODS

Prophylactic efficiency of AP was studied using a double-blind placebo-controlled method in two orphanages in St. Petersburg; the study included 204 children aging from 1 month to 4 years. The children were randomly divided into 2 groups: 104 children received AP and 100 children received placebo. Analysis of individual histories revealed the presence of this or that pathology in practically all children; SC constituted about 50% of the total sample (Table 1).

The children of the two groups and personnel closely contacted, which determined active circulation of ARVI agents. A total of 11 outbreaks caused by primarily adenoviral and rhinosyncytial infections were recorded over the total observation period. The

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TABLE 1. Characteristics of Children Groups in the Study of Prophylactic Efficiency of AP (%)

Sign	SC		HC	
	AP (*n*=46)	placebo (*n*=45)	AP (*n*=58)	placebo (*n*=55)
Birth trauma, CNS diseases	60.9	64.4	67.2	76.4
Pregnancy abnormalities	2.2	4.4	3.4	1.8
Hypotrophy, rickets	52.2	51.1	57.2	45.5
Chronic infections (including intrauterine infections)	28.2	22.2	29.3	32.7
Valvular heart defects	6.5	13.3	20.7	7.3
Dermato- or respiratory allergosis	10.9	27.8	13.8	23.6
Hepatitis B and C carriers	15.2	6.7	13.8	7.3
Anemia	20.9	6.7	22.4	12.7
Congenital diseases	10.9	4.4	5.2	9.1
Without pathologies	4.3	11.1	5.2	1.8

children received the drugs according to the prophylactic scheme (1 tablet daily) during the three winter months. In case of appearance of ARD symptoms, the prophylactic scheme was changed to the therapeutic one (1 tablet 3 times a day). In all children, general health status was evaluated daily, body temperature was measured twice a day, and clinical symptoms were recorded during ARD development. The incidence of

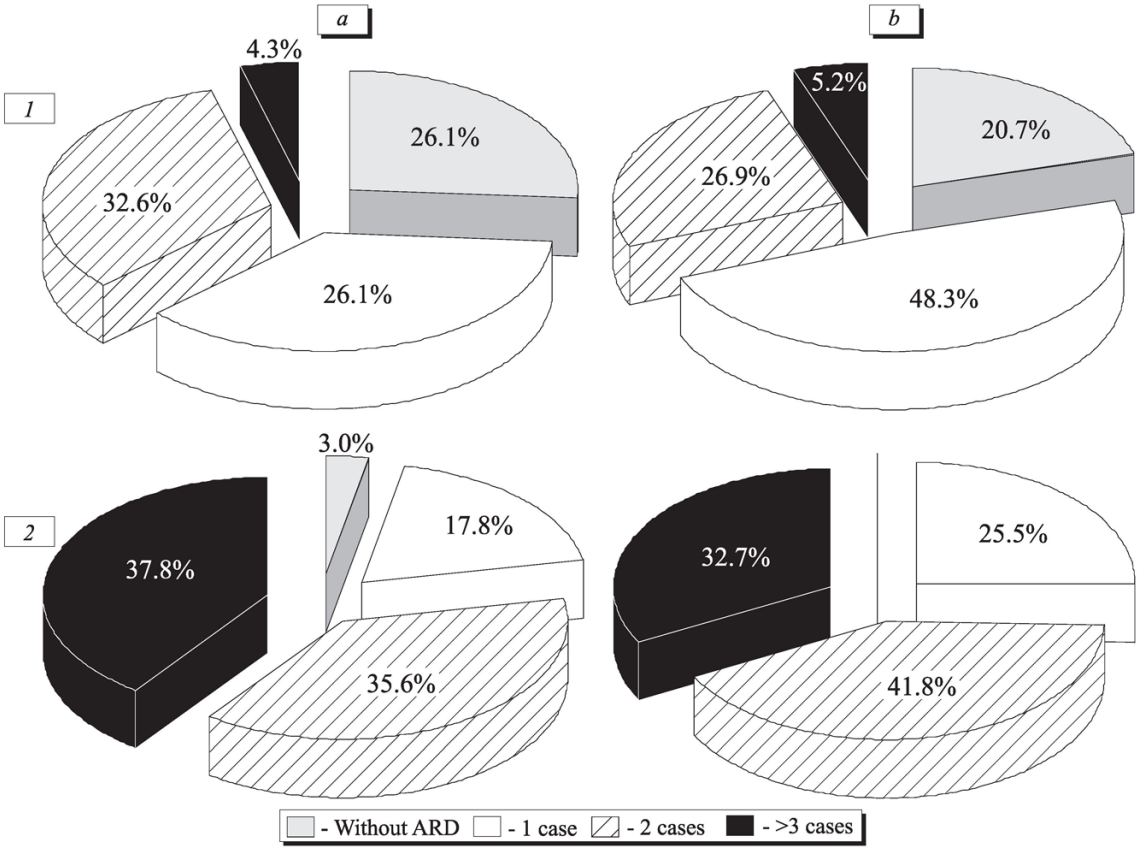

Fig. 1. Incidence of ARD in SC (*a*) and HC (*b*) against the background of AP treatment (*1*) and placebo (*2*).

TABLE 2. Prophylactic Efficiency of AP in SC (*M*±*m*)

Group		Number of ARD cases	Duration of clinical symptoms, days				
			fever	intoxication	catarrhal syndrome	acute period of the disease	complications, abs/%
SC	AP	57	2.31±0.13	2.91±0.11	7.30±0.37	8.74±0.34	3/6.5
	placebo	110	3.95±0.18	4.45±0.15	11.90±0.55	11.53±0.41	6/13.3
HC	AP	67	2.18±0.11	2.69±0.13	6.74±0.26	7.97±0.40*	3/5.2
	placebo	129	3.27±0.20	3.53±0.24	11.40±0.44	10.63±0.57	5/9.1
Total	AP	124	2.25±0.08	2.80±0.08	7.02±0.17*	8.40±0.25*	6/5.8*
	placebo	239	3.73±0.14	4.06±0.16	11.65±0.32	11.08±0.36	11/11.0

Note. *$p<0.05$ compared to placebo.

the diseases was evaluated over 2 months after test drug withdrawal.

The capacity of the test preparations to prevent the development of ARD served as the criterion of their prophylactic efficiency. The efficiency of the preparation was evaluated as follows: excellent (no ARD cases during 3-month observation), good (1-2 ARD cases with mild course), moderate (3-4 ARD cases with mild course), and poor (no effect of the preparation). The index and coefficient of epidemic efficiency of the preparation were determined [1].

Prophylactic efficiency of AP was additionally evaluated by its effect on the presence of infection in children; to this end, viral antigens were detected in smears from the nasal meatuses by express immunofluorescent method. Drug tolerance was good in the

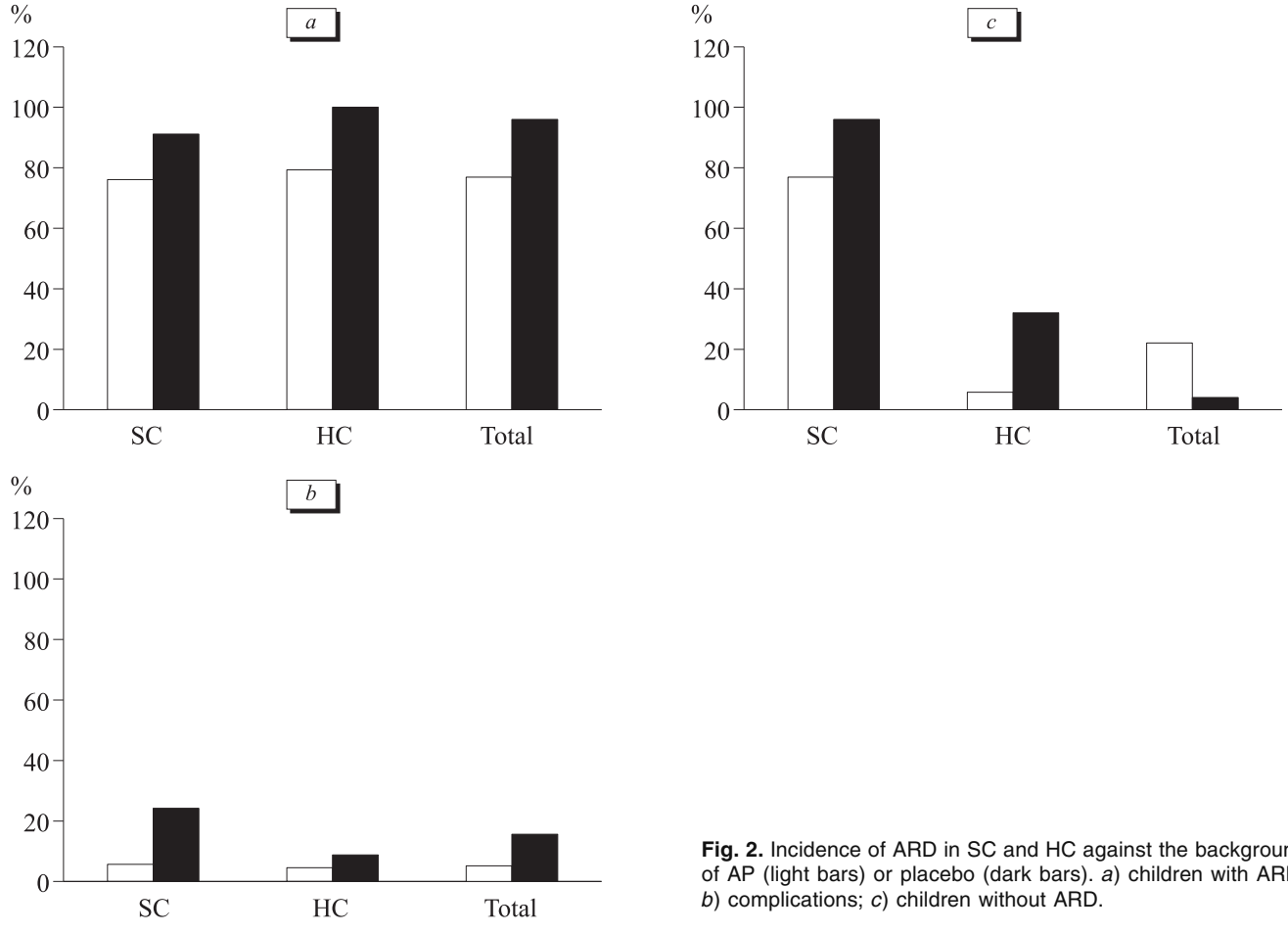

Fig. 2. Incidence of ARD in SC and HC against the background of AP (light bars) or placebo (dark bars). *a*) children with ARD; *b*) complications; *c*) children without ARD.

absence of adverse reactions and poor if these reactions appeared.

RESULTS

Three-month observation showed that treatment with AP reduced the incidence of ARD in both SC and healthy children (HC, with low incidence of infections). The incidence of infections was higher in the placebo group: 3 and more ARD cases in 32.7-37.8% children *vs*. 4.3 and 5.2% in the AP group (for SC and HC, respectively; Fig. 1). Significant efficiency of the preparation was also observed after termination of the treatment: higher incidence of infections in the placebo group (52.7-64.4% *vs*. 34.5-47.8% in AP group). Over the entire observation period, 12 SC in the AP group and 4 SC in the placebo group had no ARD (26.1 and 8.9%, respectively). Among HC, no cases of ARD were recorded in 22 children of the AP group (37.9%) and in 3 children of the placebo group (5.5%; Fig. 2). Index of efficiency was 2 and coefficient of epidemic efficiency was 50%. It should be noted that these parameters were similar in SC and HC. Clinical symptoms of ARD in the AP group were less pronounced than in the placebo group. Mild forms of ARVI with short duration of the intoxication period and catarrhal syndrome predominated (Table 2).

Routine examinations revealed no allergic reactions or other side effects of the treatment in children, including babies of the first year of life. Signs of dermatoallergosis were detected in few children in all groups.

The total incidence of detection of viral antigens in epithelial cells from the nasal meatuses obtained

TABLE 3. Incidence of Detection of Infectious Agents during Evaluation of Prophylactic Efficiency of AP (Immunofluorescent Analysis of Swabs from Nasal Mucosa)

Infection	Term of examination	SC		HC	
		AP	placebo	AP	placebo
Positive results	Before treatment	52.2*	46.7	41.4*	40.0
	During treatment	52.2*	53.3*	22.4*	34.5
	After 3 months	8.7^{+}	37.8	3.4^{+}	30.9
Influenza mono/mixed	Before treatment	6.5/2.2	6.7/8.9*	5.2/3.4*	5.5/0*
	During treatment	4.3/8.7	4.4/0	0/1.7*	0/3.6*
	After 3 months	0/0	2.2/0	1.7/0	0/0
Adeno mono/mixed	Before treatment	6.5/4.3*	2.2*/2.2*	5.2/3.4	0/5.5
	During treatment	3.0/8.7*	0/2.2*	5.2^{+}/3.4	16.4*/7.3
	After 3 months	4.3/2.2	11.1/0	3.4/5.2	5.5/9.1
Rhinosyncytial mono/mixed	Before treatment	4.3*/10.9	6.7/4.4*	12.1*/1.7*	10.9/3.6*
	During treatment	10.9*/6.5	11.1/4.4*	6.9*/3.4	3.6/1.8*
	After 3 months	0/0	6.7/0	0/0	7.3/0
Parainfluenza	Before treatment	0	0	0	1.8*
	During treatment	0	8.9*	0	1.8*
	After 3 months	0	0	0	0
Micoplasma mono	Before treatment	0	6.7	1.7	5.5
	During treatment	0	2.2	1.7	0
	After 3 months	0	4.4	6.9	1.8
Herpes mono	Before treatment	17.4*	8.9	8.6	7.3
	During treatment	0	0	0	0
	After 3 months	2.2	13.3	3.4	7.3

Note. *$p<0.05$ compared to data obtained after 3 months; $^{+}p<0.05$ compared to placebo.

from SC and HC before AP treatment was 46.7-52.2% (in the placebo group the corresponding value was 40.0-41.4%, Table 3). After administration of AP, the incidence of detection of viral antigens significantly decreased to 8.7 and 3.4% in SC and HC, respectively, compared to 37.85 and 30.9% in the placebo group; the most pronounced decrease was observed for herpes virus (stable detection of this virus is an indicator of suppressed immunity in the examinees).

Thus, 6-month observation proved prophylactic efficiency of AP, which manifested in the decrease in the percent of children with ARD and alleviation of the clinical course of the disease. This regularity was observed in both SC and HC. No side effects of AP were revealed, the drug tolerance was good in the majority of cases. Administration of AP reduced the incidence of detection of infectious agents in children. These results suggest that AP can be administered as the prophylactic means in children; the preparation can be used in children institutions among both SC and HC.

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