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Alpha Interferon Administration to Infants with Congenital Rubella

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Three infants with congenital rubella syndrome were given human leukocyte (alpha) interferon at doses of 2×10^5 to 7×10^5 U/kg per day for 10 days. A transient decrease in pharyngeal virus excretion was observed with treatment. No significant side effects were associated with the administration of human leukocyte interferon to these infants.

Despite the introduction of rubella vaccine, congenital rubella syndrome has not been eliminated (3). Although prevention of the syndrome by more effective vaccine distribution is the best approach to the problem of congenital rubella, antiviral therapy might benefit infants who are infected. Interferon is an antiviral substance with potential efficacy against RNA viruses, including rubella.

Interferon inhibits the replication of rubella virus in vitro in human fibroblast and monkey kidney cell cultures, although Desmyter et al. could not demonstrate inhibition of the virus in a rubella carrier culture established from an infected fetus (5, 10, 11). Infants with congenital rubella produce antibody to rubella virus, but interferon has not been detectable in serum from these infants (5, 7). In the only previous experience with the administration of exogenous interferon in congenital rubella, Larsson et al. (7) showed the termination of rubella viremia in a 14-month-old infant given 3×10^6 U/day for 2 weeks. Urinary excretion of the virus was not eradicated (7).

The purpose of this study was to evaluate the effect of interferon upon pharyngeal and urinary viral excretion by infants with congenital rubella by using the immunoperoxidase staining technique to quantitate viral shedding (9).

MATERIALS AND METHODS

Human leukocyte (alpha) interferon was prepared at the State Serum Institute, Helsinki, Finland, by the method of Cantell (2). Interferon was given intramuscularly every 12 h to three infants. Infant A received 2×10^5 U/kg on day 1, 7×10^5 U/kg on day 2, 5×10^5 U/kg per day on days 3 to 5, 7×10^5 U/kg per day on days 6 to 8, and 4×10^5 U/kg per day on days 9 to 10, for a total dose of 53×10^5 U/kg. Infants B and C were given 5×10^5 U/kg per day for 10 days for a total dose of 50×10^5 U/kg.

Complete blood counts and serum glutamic oxalacetic transaminase (SGOT) levels were obtained before treatment, on days 5 and 9 during treatment, and posttreatment. Sera for measurement of interferon levels were obtained 2 to 4 h after a dose of interferon. The interferon assay was performed as described previously (8).

Rubella virus isolations were done on freshly voided urine and pharyngeal secretions obtained by swabbing the posterior pharynx and rinsing the swab in 1 ml of veal infusion broth. Buffy coat cultures were done using dextran-sedimented leukocytes. All samples were stored immediately at −70°C. Cultures were performed by inoculating RK-13 and BSC-1 cells, subpassaging to BSC-1 cells at 7 days, and testing by interference and immunofluorescence. Viral titrations were done by immunoperoxidase staining of foci of infected cells in BHK-21 cultures inoculated with each specimen (9).

RESULTS

The clinical data for the infants who were treated are given in Table 1. All three infants had symptomatic congenital rubella diagnosed by viral culture in the newborn period.

Interferon levels and toxicity. Interferon was not detected in pretreatment serum samples. The serum interferon level in infant A was 3,000 U after 7 days of interferon administration at doses of 5×10^5 to 7×10^5 U/kg per day. By 2 days after treatment, serum interferon was again undetectable. Interferon was not present in the urine during treatment. The peak serum levels in infants B and C, who were given 5×10^5 U/kg per day ranged from 40 to 279 U after 5 days.

Transient side effects were observed in infant A. The SGOT rose from a pretreatment level of 82 to 688 IU by day 10. When interferon therapy was stopped, the SGOT fell to 295 IU by 4 days and returned to pretreatment levels at 10 days. The patient's leukocyte count decreased from 9,500 cells per mm^3 to 5,400 cells per mm^3 on

TABLE 1. Clinical findings in infants with congenital rubella treated with interferon

Infant	Birth wt (g)	Gestational age (wks)	Status at treatment		Current status	
			Age (mos)	Clinical problems	Age (mos)	Clinical problems
A	1,680	34	3	Microophthalmia, cataract, pulmonic stenosis	48	Deafness, impaired vision, delayed growth and development
B	2,340	42	5	Cataract, chronic pneumonia, failure to thrive	24	Deafness, chronic pneumonia, delayed growth and development
C	2,320	40	3	Microophthalmia, cataract, probable ventricular septal defect	12	Deafness, impaired vision, delayed growth and development

day 9; it was 9,900/mm^3 4 days after treatment was stopped. The platelet count fell from 500,000/mm^3 before treatment to 165,000/mm^3 on day 9, returning to 380,000/mm^3 4 days after treatment. The leukocyte and platelet counts and SGOT levels were unchanged during therapy in infants B and C. All patients were afebrile and fed well during therapy.

Effect of interferon on virus excretion. As shown in Table 2, pharyngeal cultures from all of the infants were persistently positive during and just after the treatment period. A decrease in the titers of pharyngeal virus excretion was observed in infants A and B during treatment (Table 1). The titer of virus excretion in urine was highly variable before and after treatment. Titers ranged from negative to 7×10^1 PFU/ml in infant A, from 5×10^0 to 6×10^3 PFU/ml in infant B, and from negative to 5×10^1 PFU/ml in infant C. One buffy coat culture from infant B

TABLE 2. Rubella culture results[a] in interferon-treated infants before, during, and after treatment

Infant	Pretreatment			During treatment			Posttreatment		
	Days before treatment	Pharynx (PFU)	Urine (PFU)	Day of treatment	Pharynx (PFU)	Urine (PFU)	Days after treatment	Pharynx (PFU)	Urine (PFU)
A	49	8×10^1	7×10^1	1	3×10^1	0	3	+[b]	0
	47	+	+	4	+	+	5	3×10^2	0
	42	+	0	6	0	0	23	+	0
	39	+	+	8	3×10^1	0			
	19	8×10^1	0	10	0	0			
B	59	3×10^2	5×10^0	1	2×10^2	2×10^0	10	1×10^1	2×10^0
	19	2×10^2	8.5×10^2	4	5×10^1	1×10^3	19	5×10^1	2×10^0
				8	5×10^1	5×10^3	33	1×10^1	6×10^3
				11	3×10^1	5×10^3			
C	12	+[c]	5×10^1	2	+[c]	0	7	+	ND[d]
	5	+[c]	+	5	1.8×10^1	0	24	+[c]	1.5×10^1
				10	+[c]	0	48	5×10^1	0
Positive cultures/ cultures done		9/9	6/9		10/12	5/12		9/9	5/9

[a] PFU/ml by viral titration.
[b] +, Culture was positive, but viral titration was not done.
[c] Culture was positive, but viral titration was <1:2.
[d] ND, Not done.

was positive at 2×10^0 on day 10 of treatment. A simultaneous serum interferon level was 279 U. Viral excretion persisted in all three infants for at least 6 to 12 months after treatment.

DISCUSSION

Infants with congenital rubella continue to excrete the virus for as long as 2 to 3 years after birth (4). Although the infants we treated had evidence of virus-induced pathology at birth, we felt that an attempt to interfere with viral replication was appropriate since persistent infection may cause further damage to the infant after birth (6). The prolonged shedding of rubella virus by infected infants also represents a risk to susceptible pregnant women who may be exposed to these infants. Interferon therapy may have transiently reduced viral replication in the pharynx and urinary tract in two infants (Table 2), but the virus was not eradicated from the pharynx or urine in any of the three patients we treated. Given the minimal effect of interferon upon the virus in these sites, it is unlikely that viral replication in the central nervous system or other tissues was altered. Although Larsson et al. found that viremia resolved with treatment (7), one infant in our study was viremic while receiving interferon. In our experience, rubella virus was not recovered consistently from buffy coat or urine in any of the three infants. Cultures of pharyngeal secretions were more consistently positive. However, viral titrations of these samples showed marked differences in the quantity of virus present in samples obtained at short intervals.

The elevation of SGOT seen in one infant confirmed our previous observation that high doses of interferon can alter hepatocellular function in infants (1). In contrast to adult patients, fever with interferon administration has been unusual in infants. Bone marrow suppression was not apparent in the infants with cytomegalovirus infection who were given up to 3.5×10^5 U/kg per day nor in those infants with rubella who received 5×10^5 U/kg per day for 10 days (1). The decrease in leukocyte and platelet counts seen in the infant with rubella who received up to 7×10^5 U/kg per day was comparable to the dose-related suppression seen in adult patients and was rapidly reversible with termination of therapy.

Although no final conclusions can be drawn regarding the in vivo efficacy of leukocyte interferon in congenital rubella, the results of this study substantiate our experience that infants tolerate interferon well (11). With careful monitoring of hematological and hepatic function, it should be possible to extend the effort to treat congenital viral infections using higher doses of interferon and the new preparations of interferon that are becoming available.

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