Comparison of the Efficacies of Cutaneous and Subcutaneous Administration of Tactivin for Correction of Secondary Immunodeficiency in Infants and Young Children

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A method for noninvasive administration of immunomodulators, specifically, of tactivin, has been developed. The dosage form for cutaneous applications represents a special film containing the immunocorrector tactivin. Before application the film and underlying skin site are moistened with normal saline, after which the film is held with a plaster on the skin of the forearm flexor surface for 10-12 h. The optimal dose of tactivin for applications is 100 μg. Comparative analysis showed that the efficacies of cutaneous and subcutaneous administration of tactivin to infants and young children are comparable according to immunological criteria and clinical results.

Key Words: *immunocorrection; cutaneous therapeutic systems; tactivin*

The development of infectious toxicosis (IT) in infants and young children with severe viral and bacterial infections often leads to the formation of secondary immunodeficiency. Clinically the secondary immunodeficiency state manifests itself as a predisposition to infectious diseases: such children frequently suffer from prolonged acute respiratory viral (ARVI) and other infections [1,2,10]. Our previous studies [4,6,8] showed that the level of thymic activity of the serum (TAS) at the peak of the disease is sharply reduced in such children. A low level of TAS persists during convalescence and even longer, for several months, as the follow-up showed. Moreover, previously [7,9,13] we revealed disorders of the T lymphocytic and phagocytic components of immunity and a tendency toward hyperproduction of immunoglobulin M in children with neuroinfections.

The severity of secondary immunodeficiency with the predominance of prolonged thymic insufficiency (according to the TAS test) in such children was an indication for immunocorrective therapy. Previously [6-9] we successfully used subcutaneous injections of tactivin for this purpose. The necessity for prolonged immunocorrection suggested that new dosage forms should be developed for use during the first few years of life. Parenteral administration of drugs is fraught with the potential dissemination of hazardous infections (AIDS, hepatitis B, etc.) and is traumatic and inconvenient. The transdermal route of drug administration, besides being safe, has numerous advantages: it is possible to monitor drug penetration into the blood, and its action is gradual and prolonged [3,11].

The purpose of this research was to compare the efficacies of cutaneous and subcutaneous admin-

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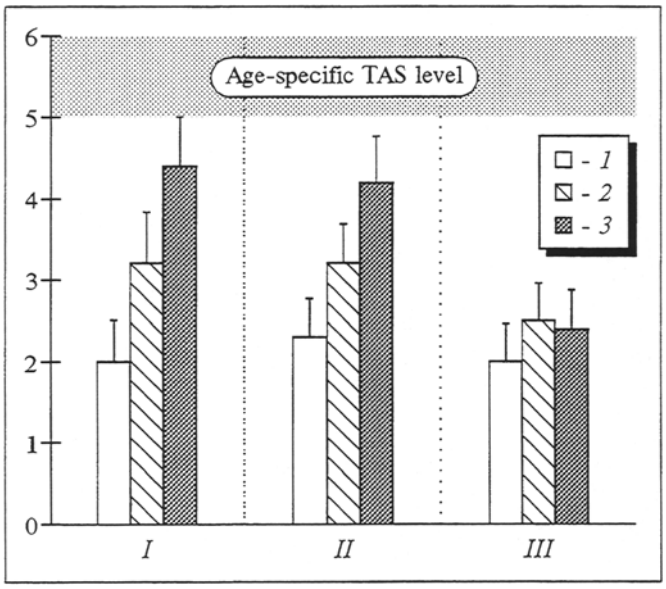

Fig. 1. Time course of TAS levels for various routes of tactivin administration. *I*) tactivin injected subcutaneously; *II*) skin applications; *III*) controls (no immunocorrection); *1*) acute period of disease (before immunocorrection); *2*) convalescence period (after immunocorrection); *3*) follow-up period.

istration of tactivin for the correction of secondary immunodeficiency in children who developed IT in the presence of severe viral and bacterial infections.

MATERIALS AND METHODS

Seventy-three children, 38 boys and 35 girls, aged 3 months to 3 years, who had had IT against the background of various viral and bacterial diseases (neuroinfections, acute respiratory diseases, and ENT diseases) were followed up. The children were divided into 3 groups: group 1 consisted of 30 children (8 with IT developing in viral and bacterial infections and 22 with neuroinfections) who were injected tactivin by the traditional subcutaneous route in a dose of 40 μg/m² body surface during the second half of the day for 5 days; group 2 was made up of 20 children (17 with noninflammatory involvement of the CNS and 3 with neuroinfections) administered tactivin cutaneously; and group 3 comprised 23 children (17 with IT in association with various infections and 6 with neuroinfections) administered no immunocorrective therapy.

The preparation for cutaneous applications consists of a special film with tactivin applied to it. Before being applied to the skin, the film and the underlying skin site are moistened with normal saline, and then the film is held with a plaster on the skin of the forearm flexor surface for 12 h. The optimal dose of tactivin for applications, 100 μg, was selected in the course of the studies.

The efficacy of immunocorrection was assessed on the basis of findings of the clinical follow-up and dynamic measurements of TAS levels [12]. Blood for analysis was collected in the acute period (during the first 2-3 days of the disease), during convalescence (on days 7-10 of the disease, and in neuroinfections after CSF sanitization), and afterwards a month or more after discharge. After a course of immunocorrective therapy, which was carried out when the acute manifestations of the disease were fading away, blood for analysis of the TAS level was collected 2-3 days after this course was over.

RESULTS

When comparing the results of cutaneous and subcutaneous use of tactivin, we studied its effect in each patient individually and averaged the results per group. We considered a result positive if the TAS level increased by 2 or more arbitrary units (AU). An increment by 1 AU was considered as a trend toward a TAS rise, while "no change" corresponded to the previous level of thymic activity. At the height of the disease TAS levels were reduced 2.5- to 3-fold in all the patients in comparison with the age-matched norm (Fig. 1). Manifest thymic insufficiency persisted during convalescence. In group 3 (without immunocorrection) measurements of the TAS level in the follow-up period after convalescence showed it to be still very low. After the first course of immunocorrection a positive effect was observed in 15 (55%) group 1 patients and in 10 (50%) group 2 patients ($p<0.05$). A trend toward a rise of the TAS level was observed in 6 (22.2%) children injected tactivin subcutaneously and in 7 (35%) in whom it was applied to the skin ($p<0.05$). In 6 (22.2%) group 1 children and in 3 (15%) group 2 patients the TAS level did not change.

TABLE 1. Comparative Efficacy of Cutaneous and Subcutaneous Administration of Tactivin

Time course of TAS level	Subcutaneous injection (n=35), %	Skin application (n=35), %	No immunocorrection (n=23), %
Positive changes	51.4	45.7	13.0*
Tendency to increase	25.7	34.3	30.4
No change	22.9	20.0	56.6*

Note. An asterisk shows a reliable ($p<0.05$) difference between the groups. n: number of examinees.

Despite a positive time course of changes, tactivin administration for 5 days (course I) did not lead to complete normalization of TAS in 80% of children injected the drug subcutaneously and in 91% of those treated with an application. Therefore, a second course of tactivin was administered to some children 2-4 weeks after the first one, with the same dose of the agent applied daily for 5 days.

The results of the two routes of tactivin administration were fully comparable both in the groups under study and in individual patients (Fig. 1, Table 1). Table 1 shows that a positive effect was attained in 51.4% of cases with subcutaneous and in 45.7% with cutaneous application of the drug. A trend toward a rise of the TAS level was observed in 25.7% of cases of subcutaneous and in 34.3% of cutaneous application of tactivin. In 22.9% of group 1 and in 20% of group 2 patients the TAS levels did not change.

Only in one-third of the patients was an increase of the TAS level to the age-specific norm attained, irrespective of the route of administration. However, even in the case of persistent thymic insufficiency an appreciable reduction of infectious morbidity was observed.

In the course of the investigation we were struck by the different types of patient responses to tactivin immunocorrection, regardless of the route of administration. As is seen from Fig. 2, there was a group of children in whom the very first course of tactivin caused TAS to rise practically to the normal level (*I, II*). In another group (*III, IV*) thymic activity normalized after a repeated course of immunocorrection. Then there were some patients in whom just a tendency toward an increase of the TAS level was observed after a course of tactivin, but no further increase occurred in the follow-up period after convalescence. And, finally, some children (4%) did not respond to immunocorrection, no matter what the route of drug administration (*V*).

We should emphasize that no cases of local irritation from the tactivin applications or general side effects of the drug injected subcutaneously were observed in the course of the investigation. Hence, our study proved the feasibility and efficacy of cutaneous applications of tactivin in young children. This dosage form is quite convenient and may be recommended for immunocorrective therapy in a hospital or outpatient setting.

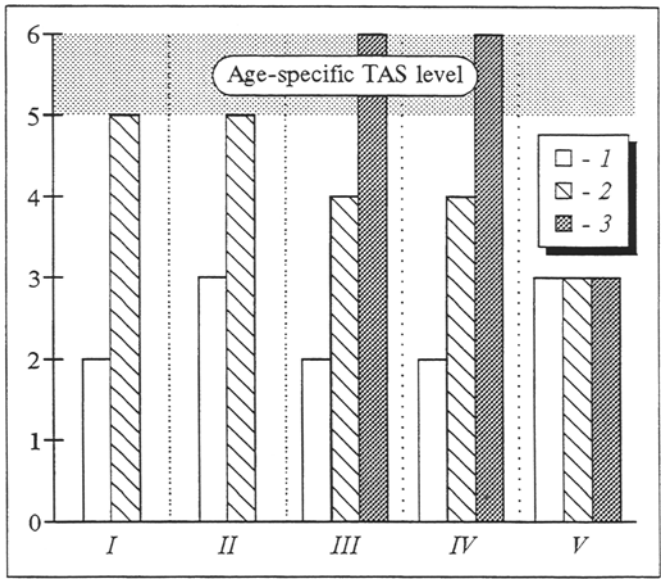

Fig. 2. Time course of TAS levels in individual patients. *1*) before therapy; *2*) after the first course of immunocorrection; *3*) after the second course of immunocorrection. *I*) patient S., aged 7 months, with viral meningoencephalitis, injected tactivin subcutaneously; *II*) patient K., aged 2 years, with ARVI and brain edema, given tactivin cutaneously; *III*) patient V., aged 18 months, with ARVI and encephalitis reaction, administered skin applications of tactivin; *IV*) patient G., aged 3 years, with ARVI and brain edema, given tactivin cutaneously; *V*) patient S., aged 2 years 10 months, with ARVI and encephalitis reaction, injected tactivin subcutaneously.

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