Treatment of Systemic Scleroderma with Fucidine with Regard to Some Free Amino Acids Contents before and after Therapy

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In 7 patients with systemic scleroderma and acroscleroderma improvement was observed after the administration of fucidine. In the same time 4 amino acids contents, which had been abnormal prior to the therapy, normalized. (Received May 23, 1983.)

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Systemic scleroderma so far constitutes serious therapeutic problems. The application of penicillin or cuprenil is limited, because of the rather frequent allergy to these drugs and such was the case with our patients with scleroderma. While searching for an other antibiotics for acute dermatological symptoms, lung alterations and persistent high fever, an uncommon drug—fucidine was used. After about three weeks administration (dose of 1 g/day) apart from marked improvement of the general condition and quick temperature recurrence to normal, our attention was drawn to the pronounced regress of both induration and tension of the skin on the face and upper extremities. As the treatment was continued for the next two weeks the improvement was so conspicuous that no doubt could arise as to the fact. The observation encouraged us to administer fucidine in six other cases with progressing scleroderma.

MATERIAL AND METHODS

Attempts to treat with fucidine were carried out in seven female patients with generalized scleroderma, admitted to the I Chair and Clinic of Dermatology, Silesian Academy of Medicine, Katowice. In these patients aged from 17 to 57 years, of whom 5 suffered from scleroderma diffusa and 2 from

acroscleroderma, the shortest duration of the disease was 3 months and the longest 16 years. In all the patients the intensity of the disease was very marked different for each individual affecting internal organs (lung, eosophagus, bones). The duration of the treatment with fucidine ranged from 30 to 80 days 1.0 g/day.

In all these patients before the treatment and after 4 to 10 weeks of fucidine administration as well as in six controls analyses of free amino acids in blood serum were carried out.

The analyser type AAA 881 made by Mikrotechna-Praha, adjusted to one column system after Hamilton (1) with ion exchange resin type Beckman W-3 and with ammonia filtration system described by Melançon and Tayco (2) was used in the study.

RESULTS

All the patients improved except one, the youngest with a 3 months' course of the disease. Changes in amino acids contents in blood serum are shown in Table I.

Table I. *Free amino acids contents in healthy persons and sclerodermic patients blood serum (% mol)*

	Healthy persons (n=6) $\bar{x}_1$	Sclerodermic patients (n=7)	
		Before fucidine treatment $\bar{x}_2$	After fucidine treatment $\bar{x}_3$
Taurine (Tau)	2.40	6.19	5.78
Aspartic Acid (Asp)	0.54±0.07	2.07±0.39	0.90±0.48
Threonine (Thr)	5.36	4.81	3.79
Serine (Ser)	5.37	6.37	4.07
Asparagine (Asn)	1.24±0.51	0.26±0.45	1.98±0.55
Glutamic Acid (Glu)	6.42±2.79	11.34±3.83	6.06±1.68
Glutamine (Gln)	15.18±2.07	3.16±2.34	12.25±2.15
Proline (Pro)	7.45	6.30	5.96
Glycine (Gly)	9.55	11.95	12.69
Alanine (Ala)	10.76	11.02	10.16
Citrulline (Cit)	1.35	0.71	0.83
Aminobutyric Acid (Aba)	0.62	0.40	0.51
Valine (Val)	7.73	6.15	6.12
Cystine (Cys)	–	–	–
Methionine (Met)	0.74	1.20	0.89
Isoleucine (Ile)	1.74	1.31	1.17
Leucine (Leu)	3.89	5.29	4.46
Tyrosine (Tyr)	2.02	2.24	2.64
Phenylalanine (Phe)	2.25	3.01	2.99
Ornithine (Orn)	4.84	4.87	4.26
Lysine (Lys)	5.64	6.11	6.47
Histidine (His)	2.75	3.17	3.78
Arginine (Arg)	2.19	2.09	2.29

For Asp	$\bar{x}_1 \neq \bar{x}_2$	$p<0.001$	For Asn	$\bar{x}_1 \neq \bar{x}_2$	$p<0.01$
	$\bar{x}_1 = \bar{x}_3$			$\bar{x}_1 \neq \bar{x}_3$	$p<0.05$
	$\bar{x}_2 \neq \bar{x}_3$	$p<0.001$		$\bar{x}_2 \neq \bar{x}_3$	$p<0.001$
For Glu	$\bar{x}_1 \neq \bar{x}_2$	$p<0.05$	For Gln	$\bar{x}_1 \neq \bar{x}_2$	$p<0.001$
	$\bar{x}_1 = \bar{x}_3$			$\bar{x}_1 = \bar{x}_3$	
	$\bar{x}_2 \neq \bar{x}_3$	$p<0.001$		$\bar{x}_2 \neq \bar{x}_3$	$p<0.001$

The authors have values in detail of each patient before, after short, after interruption and after long treatment.

DISCUSSION

In 7 observed cases of systemic scleroderma it has been stated that on administration of fucidine for 4 to 10 weeks the progress of the disease was stopped and moreover in 6 patients the existing alterations have partially regressed as skin and subcutaneous tissue were slightly less indured and fingers flexing and straightening were easier. In 3 patients small trophic ulcerations on finger pulps have healed. Simultaneously the regress of subjective symptoms in the form of general weakness, dyspnea connected with effort, articulation ache and others were noted.

The relatively slightest clinical improvement was achieved in the youngest patient age 17, with a 3 months' anamnesis.

Fucidine belongs to the so-called "minor antibiotics" (3) and its application is usually limited to infections caused by penicillin resistant staphylococcus or in cases of allergy to penicillin.

Fucidine structure differs from other antibiotics as it has the steroid structure. The mechanism of the effect of this drug as an antibiotic consists in hampering bacterial protein synthesis by blocking in the course of the process the translocation stage thus enabling the decomposition of complex G-GTP-ribosome factor (3, 4).

The amino acids which play a role in collagen biosynthesis belong in the first place hydroxyproline (Hyp), hydroxylysine (Hyl), and proline (Pro). So far the search for effective drugs in the therapy of systemic scleroderma, a collagen disease of unknown pathomechanism, has been based on either the proved or the alleged effect hampering collagen synthesis. In such bearing several investigations and clinical attempts were made with the following drugs: D-penicillamine (4), steroids, immunosupresors, chelating agents (5), dextro-thyroxine (6).

Personal investigations on the analysis of amino acids in the 7 reported cases of scleroderma in the first stage of therapy with fucidine (4 to 10 weeks) have drawn our attention particularly to the behaviour of 4 out of 23 amino acids under study. The initial findings in all the cases as compared with the controls revealed changes in aspartic and glutamic acids as well as in asparagine and glutamine contents. Prior to treatment increased contents of aspartic and glutamic acids and the parallelly decreased content of asparagine to trace value or no asparagine at all and the reduced content of glutamine were noted. Statistical studies carried on the base of Student's test show that differences between the mean contents of aspartic and glutamic acids, asparagine and glutamine labelled initially in the patients (prior to the administration of fucidine) and in the controls are in general highly significant ($p<0.01$–0.001).

Findings after the resumed therapy with fucidine revealed in these patients the recurrence to normal values viz. highly significant decrease in aspartic and glutamic acids contents as well as increase in asparagine content and distinct increase in glutamine content. The curve of increased asparagine content and particularly that of glutamine in the course of treatment with fucidine show some regularity and correlation with the duration of the drug administration till normal values were achieved. When the first stage of treatment had been completed in two cases that were checked up longer than any others, during the over two months lasting interval reappeared the decrease in asparagine and glutamine with the simultaneous increase in aspartic and glutamic acids contents which were analogous to values recorded before the treatment with fucidine.

The effect achieved in normalizing the 4 amino acids in question in blood serum in 7 cases of scleroderma after the administration of fucidine as well as the reappearance of disturbed values of these amino acids after some weeks' interval in the therapy in two patients with the simultaneous regress of clinical alterations indicate the significance of fucidine in the treatment of generalized scleroderma.

In the available literature we have encountered only Asboe-Hansen's report (7) on the attempt to treat systemic scleroderma among other methods with the so-called "mixed therapy" comprising glutamine associated with chlorpromasine.

The role of the amino acids in the pathomechanism of systemic scleroderma, which are discussed in the present paper, and the part fucidine plays in the aspect of therapeutic effect will be the topic of our further biochemical and clinical investigations.

REFERENCES

1. Hamilton PB. Ion exchange chromatography of amino acids. A single column high resolving, fully automatic procedure. Anal Chem 1963; 35: 2055–2060.
2. Melançon SB, Tayco J. Single column amino acids analysis using lithium buffers and an ammonia filtration system. J Chromatogr 1971; 63: 404–407.
3. Kuryłowicz W. Antybiotyki. p. 152. PZWL Warszawa 1979.
4. Uitto J, Helin P, Rasmussen OG, Lorenzen I. Skin collagen in patients with scleroderma. Ann Clin Res 1970; 2: 228–232.
5. Blumenkrantz N, Asboe-Hansen G. Effect of chelating agents on the biosynthesis of collagen. Acta Derm Venereol (Stockh) 1973; 53: 94–99.
6. Asboe-Hansen G. Treatment of generalized scleroderma with inhibitors of connective-tissue formation. Acta Derm Venereol (Stockh) 1975; 55: 461–465.
7. Asboe-Hansen G. Neue Entwickling der Pathologie, Pathophysiologie und Therapie der systemischen Sclerodermie. Hautarzt 1980; 31: 584–587.