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Clinical study of cutaneous response to a new rubefacient - Trafuril

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A CLINICAL STUDY OF CUTANEOUS RESPONSE TO A NEW RUBEFACIENT - TRAFURIL

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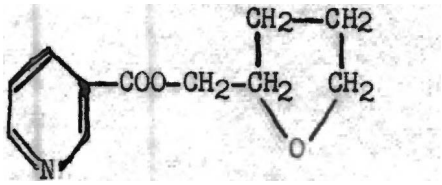
INTRODUCTION

Although clinical diagnosis and evaluation of rheumatic activity based on Jones'[1] criteria have been greatly aided by such non-specific tests as antistreptolysin-O[2], antihyaluronidase[3], and C-reactive protein[4,5] determinations, there is still needed a single, specific test for rheumatic fever.[6]

In 1941 a substance was developed by Gross and Merz[7] which was found to cause a local vasodilitation of deep tissues with production of an effective hyperemia and relief of pain in the treatment of muscular rheumatism.[8,9] A 5% water miscible cream of the new rubefacient, tetrahydrofurfuryl ester of nicotinic acid, Trafuril*, was found by Nassim and Banner[10] to give a cutaneous hyperemic and/or edamatous reaction when applied to the skin of normal subjects but failed to do so in five patients with active rheumatoid arthritis. The chemical formula of Trafuril is:



This led Streitfeld and Saslaw[11] to test the effect of inunction with Trafuril on 337 children with and without

* Kindly supplied by Ciba Pharmaceutical Products Inc., Summit, N.J.

active rheumatic fever. They found positive correlation between clinical evaluation of rheumatic activity and the type of skin response observed occurred in 90.5% of all the patients tested. Correlation was lacking in 2.7% and equivocal in 6.8%.

The observations of these two groups seem to indicate that this cutaneous reaction is of some value in the diagnosis and evaluation of activity in rheumatic fever and rheumatoid arthritis but not in differentiating these two conditions from each other.

In an effort to further evaluate Trafuril as a diagnostic tool and, perhaps, indirectly afford additional clues as to the etiology of the rheumatic process, it was decided to observe responses to the ointment in both adults and children with and without rheumatic activity.

This is a report of our results in 100 subjects.

TABLE I

RESPONSE TO TRAFURIL OF 15 PATIENTS WITH RHEUMATIC FEVER

Initials	AGE	SEX	RACE	Clinical Diagnosis	Treatment at Time of Test	Response*	ESR	Hbg.	WBC
K.C.	10	F	W	Active rheumatic fever with CHF (Poss. nephrotic stage glomerulonephritis)	Digitoxin Bicillin Diamox	D		15.0	10,950
M.B.	8	M	N	Active rheumatic fever	Aspirin 60 gr/day	A	22	13.2	9,000
23 days later				Active rheumatic fever	"	A	16	13.2	9,000
H.A.	23	M	W	Active rheumatic fever	None	N	18	14.8	5,600
M.E.	11	M	W	Rheumatic fever suppressed by medication	Cortisone	N	20	15.2	10,800
L.R.	36	F	W	Active rheumatic fever	Cortisone	N	28	12.5	14,100
30 days later				Rheumatic heart disease; ?active rheumatic fever: ? SBE	Supportive - no cortisone	N	42		11,500
L.O.	17	F	W	Inactive rheumatic fever	None	N	13	15.0	10,700
D.L.	15	F	W	Inactive rheumatic fever	None	N	10	14.8	11,300
C.B.	14	M	W	Inactive rheumatic fever	Na Salicylate Penicillin	N	4	17.0	6,700
M.F.	14	F	N	Inactive rheumatic fever	None	N	18	13.0	10,500
P.L.	28	M	W	Inactive rheumatic fever	None	N	6	17.0	5,800
D.G.	8	M	W	Heart disease, possibly rheumatic fever	None	A	45	4.8	7,200
M.Z.	8	F	W	Possibly rheumatic fever	None	N	4	12.5	10,000
E.S.	44	M	W	Rheumatic heart disease Portal cirrhosis	None	N	20	15.2	7,800
N.M.	23	F	W	Rheumatic heart disease	Digitoxin	N		13.2	7,000
J.M.	78	F	W	Myocardial Infarction Rheumatic heart disease	Supportive	N	42	13.8	5,200

* N-Normal
A-Abnormal
D-Doubtful

TABLE II

RESPONSE TO TRAFURIL OF 9 PATIENTS WITH RHEUMATIC ARTHRITIS

Initials	AGE	SEX	RACE	Clinical Diagnosis	Treatment at Time of Test	Response	ESR	Hbg.	WBC
L.J.	2	M	W	Acute rheumatoid arthritis	Aspirin 10 gr/day	A	19	12.0	8,500
D.H.	54	M	W	Acute rheumatoid arthritis	Aspirin 90 gr/day	A	-	-	-
D.H.	43	F	W	Acute rheumatoid arthritis	None	D	45	13.2	14,700
J.R.	14	M	W	Acute rheumatoid arthritis	None	N	34	15.0	9,000
T.K.	19	M	W	Acute rheumatoid arthritis	None	N	24	14.0	10,800
7 days later				Acute rheumatoid arthritis	Na salicylate	A	24	-	-
A.D.	2	F	W	Acute rheumatoid arthritis	None	A	30	12.5	11,800
J.L.	61	M	W	Acute rheumatoid arthritis	Cortisone 50 mg/day	N	20	14.4	9,400
A.P.	55	F	W	Inactive rheumatoid arthritis Pleuritis	Penicillin	N	30	14.4	7,800
E.G.	61	M	W	Emphysema Rheumatoid and Osteo-arthritis	Aspirin 60 gr/day Penicillin KI	N	18	13.6	13,900

TABLE III

RESPONSE TO TRAFURIL OF 76 PATIENTS WITH NON-RHEUMATIC DIAGNOSES

Initials	AGE	SEX	RACE	Clinical Diagnosis	Treatment at Time of Test	Response	ESR	Hbg.	WBC	Cultures
K.K.	9	F	W	Normal	None	N	-	-	-	-
D.B.	10	M	W	Normal	None	N	-	-	-	-
L.B.	9	M	W	Normal	None	N	-	-	-	-
W.M.	4½	M	W	Congenital heart	None	N	20	13.2	11,700	-
S.R.	23	M	W	Congenital heart	None	N	-	22.0	-	-
R.L.	6	M	W	Congenital heart	None	N	-	-	-	-
S.B.	3½	M	W	Congenital heart	Supportive	N	0	19.2	6,000	-
A.R.	12	M	W	Congenital heart	Combiotic	N	0	19.0	9,200	-
T.M.	7	M	W	Chronic Glomerulonephritis	Supportive	N	41	14.8	6,900	-
C.S.	7	M	W	Tonsillitis	Penicillin	A	45	13.6	5,500	Beta-hemolytic strep.
5 days later				Clinically well	None	N	-	-	-	-
J.S.	16mo	F	W	Follicular tonsillitis	Terramycin	N	-	11.5	18,500	-
5 days prior							-	-	-	Strep. viridans
T.K.	3	M	W	Laryngeal-tracheal bronchitis	None	N	-	13.0	12,500	-
30 days prior							-	-	-	Strep. viridans
C.R.	1	M	W	Laryngeal-tracheitis Possible cerebral palsy	Achromycin	N	-	11.5	12,500	-
5 days prior							-	-	-	Beta-hemolytic strep.

TABLE III, CON'D.

RESPONSE TO TRAFURIL OF 76 PATIENTS WITH NON-RHEUMATIC DIAGNOSES

Initials	AGE	SEX	RACE	Clinical Diagnosis	Treatment at Time of Test	Response	ESR	Hbg.	WBC	Cultures
G.P.	48	F	W	Diffuse collagen disease Polyarteritis nodosa(?)	Cortisone	N	34	11.5	18,300	-
V.S.	8	M	I	Streptococcal pyoderma	None	A	51	12.2	11,100	-
J.McM.	12	F	W	Ulcerative colitis	None	A	-	11.2	12,300	-
22 days later				Ulcerative colitis	None	A	-	-	-	-
M.C.	49	F	W	Hypertension Cholelithiasis	None	A	26	14.0	7,300	-
M.K.	6mo.	M	W	Erythema multiforme Pneumonitis	Terramycin	N	-	-	-	-
2 days prior							-	-	-	Strep viridans
D.C.	19	F	W	Erythema multiforme	None	N	11	15.4	10,300	-
O.C.	85	M	W	Gastric ulcer	Transfusion	D	-	8.4	5,800	-
H.O.	83	F	W	Myasthenia gravis Osteoarthritis	Prostigmine Belladonna	D	46	14.8	6,400	-

* 55 subjects with miscellaneous diagnoses had typical reactions

* 3 fractures, 3 osteoarthritis, 4 diabetes mellitus, 3 duodenal ulcers, 6 carcinomas, 2 burns, 2 meningitis, 2 hypertension, 2 URI, 1 each of chronic peribronchitis, epiphysitis of hip, hemophilia, epilepsy, esotropia, pneumonia, headaches of unknown etiology, angina pectoris, asthma, laceration, mental diviaion, cerebral palsy, congenital cataracts, esophageal stricture, urinary infection, atresia of bile ducts, bowel obstruction, hernia, appendiceal abscess, chronic appendicitis, empyema, vocal cord paralysis, p. op. cholecystectomy, toxic nodular goiter, viral pharyngitis, Laennec's cirrhosis, multiple trauma, swallowed coin.

MATERIAL AND METHODS

The study covered 100 adults and children, 6 months to 85 years of age, including 4 Negroes and 1 American Indian. They were classified in 3 groups according to clinical diagnosis of rheumatic fever, rheumatoid arthritis, or non-rheumatics (Tables I, II, and III). These cases were in the hospital or out-patient department of the University of Nebraska Hospital (Omaha, Nebraska).

All tests were performed and interpreted by the author without knowledge of the clinical diagnoses which were made independently by the clinical staffs of these institutions.

The subjective responses of the patient, body temperature at time of test, sedimentation rate, hemoglobin, and white blood count were also recorded.

Technique: The technique of the test was the same as described by Streitfeld and Saslaw.[11] A small amount of 5% Trafuril ointment, in a vaseline-lanolin base, was gently rubbed with 35 circular strokes into an area 1½ inches in diameter on the volar aspect of the forearm about an inch above the wrist. A finger cot was used for protection of the physician in performing the test.

As a control, the ointment base minus the Trafuril was applied in the same manner as the test ointment, either on the

forearm above the test area or on the corresponding site the other forearm.

Test Readings: Readings were also made in accordance with the criteria stated by Streitfeld and Saslaw[11] as follows:

The skin under the test ointment and in the surrounding area (spread zone) was observed for hyperemia and edema at 10, 20 and 30 minutes after application of the Trafuril ointment, and compared with the control. After a half hour, the ointments were removed by gently wiping repeatedly with alcohol pledgets, and a final reading made. However, if intense hyperemia developed before 30 minutes, the ointment was removed at once, and a reading made. This rapid hyperemic response was also noted more commonly in this series in infants under 2 years of age.

Skin color changes were graded as follows:

0, blanching, without edema

-, no visible color change

$\pm$, barely perceptible hyperemia

$+$ to $++$, hyperemia of increasing intensity

The width of the spread zone reaction also was recorded.

A normal response consisted of the development of hyperemia within 30 minutes: in the ointment area, $+$ to $++$; and in the spread zone, - to $++$, extending in some cases to 1½ inches beyond the site of application. Edema, with or without

hyperemia, also occurred. Usually, as edema developed, emia faded, often resulting in blanching.

When hyperemia was barely perceptible (±) in the ointment zone and + to ++ in the spread zone extending more than ¼ inch without edema, this response was considered normal.

A response was abnormal if blanching or failure of the skin to become hyperemic at the ointment site occurred without edema by the end of the 30-minute period. Occasionally, a barely perceptible (±) erythema developed at 10 minutes, fading out completely by the end of the 30-minute test period. When hyperemia occurred in the spread zone, it was found to extend no more than ¼ inch beyond the ointment area when barely perceptible (±), or 1/8 inch when of + intensity.

Doubtful responses were recorded when there was no edema but a ± hyperemia persisted in the ointment zone with a - to + hyperemia of no more than 1/8 inch in the spread zone. These also had no subjective sensation.

Daylight was found to be best for reading the responses. In Negroes, particularly, the interpretation often could be made only by carefully comparing the test with the control area after removal of the ointments at the end of 30 minutes.

TABLE IV

CORRELATION OF SKIN RESPONSE WITH PRESENCE OR ABSENCE OF RHEUMATIC ACTIVITY, BASED ON THE PREMISE THAT ABNORMAL RESPONSE SIGNIFIES RHEUMATIC ACTIVITY

Rheumatic Status	No. Cases	Skin Response Observed	Positive Correlation No.	%	Failures of Correlation No.	%	Equivocal Correlation No.	%
Active*	10	Abnormal	5**	50%	-	-	-	-
		Normal	-	-	3	30%	-	-
		Doubtful	-	-	-	-	2	20%
Inactive or Non-Rheumatic	85	Abnormal	-	-	4	4.7%	-	-
		Normal	79	92.9%	-	-	-	-
		Doubtful	-	-	-	-	2	2.4%
Active Suppressed by Cortisone	3	Normal	3	100%	-	-	-	-
		Abnormal	-	-	-	-	-	-
Activity Indeterminate	2	Normal	-	-	-	-	1	50%
		Abnormal	-	-	-	-	1	50%
Totals	100		87	87%	7	7%	6	6%

* Including 3 rheumatic fever and 7 rheumatoid arthritis.
** Including 1 which gave a typical response earlier

RESULTS

As shown in Tables I, II, and III, there was no correlation of sedimentation rate, hemoglobin, or leukocyte count with the type of response to Trafuril. Only four patients had oral temperatures of over 100^0 F. Of these there were three normal responses and one abnormal response; no conclusion as to effect of temperature on the test could be reached.

Subjectively, a few of the patients experienced mild itching and/or a feeling of warmth at the site of application.

Tables I, II, and III list the diagnoses of the 100 patients with their responses to Trafuril. Table IV is a summary of skin responses correlated with the presence or absence of rheumatic activity, based on the premise that rheumatic activity as determined by Trafuril did not differentiate between rheumatic fever and rheumatoid arthritis, and, therefore, these two diseases were considered together. It was also assumed that active rheumatics suppressed by cortisone at the time of testing resulted in a normal response.

On this basis, Table IV shows a positive correlation in 50% of the active rheumatics, 92.9% of the inactive or non-rheumatics, and 87% of the total series. In these patients, the observed skin response conformed to the presence or absence of rheumatic activity. Three (100%) of the patients

in the active group on cortisone therapy gave a positive correlation; i.e., a normal reaction.

Equivocal results were obtained in 6 (6%) of the total. In these patients, the objective evidence of 2 was insufficient to permit a definite estimate of their rheumatic activity and consequently no conclusion couldbe drawn as to the significance of their skin response. In 4 others the skin test was "doubtful" and, therefore, no conclusion as to its significance could be made.

There was no correlation between the response to skin test and the clinical estimate of rheumatic activity in 3 (30%) of the active group and 7(7%) of the entire group of patients.

DISCUSSION

The high correlation between the presence or absence of active rheumatic disease and the type of skin response observed in this series of patients appears to corroborate the earlier reports of Nassim and Banner[10] and Streitfeld and Saslaw.[11] It also concurs with observations of the latter authors that the response does not differentiate rheumatic fever from rheumatoid arthritis. This coincides with the theory that these two diseases are basically similar, if not the same.[12]

All patients receiving cortisone at the time of testing were found, as was anticipated, to give normal reactions

regardless of rheumatic activity. It is unfortunate that one patient with a diagnosis of "diffuse collagen disease" was not tested when not receiving cortisone as an abnormal response might be expected if these processes are all interrelated. One patient with a diagnosis of active rheumatic fever gave a normal response while on cortisone therapy but 4 weeks later after cortisone was discontinued her response remained normal. However, clinical diagnosis at that time was rheumatic heart disease, active rheumatic fever in question and possible subacute bacterial endocarditis. This same patient on repeat testing had a delayed extensive hyperemic response, as observed by Nassim and Barmer[10], 20-30 minutes after ointment had been removed and read as normal.

This change in response to normal did not occur in patients with active diagnosis receiving aspirin. One active rheumatic fever patient received 60 gr. daily over a period of 23 days and response remained abnormal. One rheumatoid patient developed an abnormal response while on sodium salicylate 7 days after first test when he had been questionably active. Two other rheumatoids had been receiving 10 gr. and 90 gr. daily over a long period and gave abnormal responses.

As was noted in 3 cases of Streitfeld and Saslaw[11] the abnormal response observed in rheumatic patients was also ob-

tained in 1 case of tonsillitis from whom beta-hymolytic streptococci were isolated on the day of testing. Five days later, after receiving penicillin therapy, the patient was clinically well and had reverted to a normal skin response. One patient, an American Indian, with severe streptococcal pyoderma also gave an abnormal response but, unfortunately, no culture was reported.

Five congenital hearts, one case of glomerulonephritis and 2 cases of erythema multiforme gave normal responses. At the present time there is no explanation for the abnormal responses in a 12 year old girl with ulcerative colitis and a woman with hypertension and cholelithiasis.

Unfortunately only a small number of active rheumatics were available for this series and many additional subjects will need to be studied before final evaluation of the value of Trafuril as a screening test for active rheumatic disease can be made.

It is not known whether the dilator effect of Trafuril is direct or due to the release of a dilator substance.[8] It is not a histamine reaction according to Stark-Mittelholzer[13] or acetylcholine effect according to studies of Gross and Merz.[14] There is indication that a response similar to those produced by Trafuril may be shown by other compounds of nicotinic acid.[10]

Any one or any combination of the following theories as to the mechanism of this reaction may prove to be an important part of the basic alterations in rheumatic disease:

1. Altered capillary resistance in patients with rheumatic activity has been noted by Brown and Wasson[15] and others.

2. Disturbances in normal nicotinic acid metabolism may occur. Nicotinic acid is an essential part of coenzymes I (DPN) and II (TPN) which are concerned with cellular respiration and carbohydrate metabolism. Altered carbohydrate metabolism in rheumatic fever and rheumatic arthritis has been suggested by several workers; for example, Haydu[16] has shown clinical improvement of rheumatic arthritic cases receiving insulin. Shetlar[17] has observed serum polysaccharide elevation during rheumatic activity and, incidentally, a decrease of this component when patients were under cortisone therapy. Heparin, a sulphated polysaccharide, is known to be inactivated by the blood of rheumatic fever patients (Abrahams, Glynn, and Leowi).[18] They suggest that there is an impairment of other properties of heparin, such as inhibition of hyaluronidase and streptococcal ribonuclease, and a strong affinity for complement. Bywaters[19] has noted in active rheumatic fever a delayed restitution of polysaccharide following enzymatic breakdown in vivo. These alterations await further clarification.

3. Disturbances in hyaluronic acid metabolism are suggested which may cause either an increased barrier to drug absorption or an increased diffusion of the drug and its products. Meyer[20], Kahn and Goldring[21], and Bywaters[19] have suggested disorders in these processes. It is of interest that hyaluronic acid is an important constituent of connective tissue, the seat of the rheumatic processes. Of correlative interest is the fact that hemolytic streptococci produce hyaluronic acid and hyaluronidase[22]; and that cortisone and ACTH have been demonstrated to neutralize the spreading action of hyaluronidase in tissue (Gregg and Gregg).[23]

The present study may provide direction for further investigation into the etiology of these diseases as well as indicating a possible screening test for the determination of rheumatic and rheumatoid activity.

SUMMARY

1. The effect of cutaneous application of an ointment containing 5% tetrahydrofurfuryl ester of nicotinic acid (Trafuril) was studied in 100 adults and children. The clinical evaluation of each subject and the skin test were performed independently.

2. It was found that 92.9% of 85 subjects who were normal, inactive or non-rheumatic, and all patients on cortisone therapy, regardless of rheumatic activity responded by localized

cutaneous hyperemia and/oredema (normal reaction).

3. Five of 10 patients with active rheumatic fever or rheumatoid arthritis failed to show a normal response. Their response (abnormal) consisted of either blanching, failure to react, or barely perceptible hyperemia.

4. Positive correlation between clinical evaluation of rheumatic and rheumatoid activity and the type of skin response observed occurred in 87% of all the patients tested. Correlation was lacking in 7% and equivocal in 6%.

5. The abnormal response to Trafuril was also observed in streptococcal tonsillitis and pyoderma as well as in rheumatic activity.

6. This reaction may be useful as a screening device for rheumatic and rheumatoid activity, and may be of assistance in determining the etiology of these diseases.

7. Although this study was limited to a small number of active rheumatic subjects, it is felt that the findings concur with those of previous investigators and that further investigation of this reaction is warranted.

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BIBLIOGRAPHY

1. Jones, T. D.: The Diagnosis of Rheumatic Fever, J. A. M. A. 126:481, 1944.

2. Rothbard, S.; Watson, R. F.: Swift, H. F., and Wilson, A. T.: Bacteriologic and Immunologic Studies on Patients with Hemolytic Streptococcal Infections as Related to Rheumatic Fever, Arch. Int. Med. 82:229, 1948.

3. Swift, H. F.: The Etiology of Rheumatic Fever, Ann. Int. Med. 31:715-738, 1949.

4. Hill, A. G. S.: C-Reactive Protein in the Chronic Rheumatic Diseases, Lancet 2:807-811 (Nov. 3) 1951.

5. Hill, A. G. S.: C-Reactive Protein in Rheumatic Fever, Lancet 2:558-560 (Sept. 20) 1952.

6. McCarty, Maclyn: Present Status of Diagnostic Tests for Rheumatic Fever, Ann. Int. Med. 37:1027, 1952.

7. Gross, F., and Merz, E.: Pharmakologische Eigenschaften des "Trafuril", eines neuen Nikotinsaureesters mit hyperamisierender Wirkung, Schweiz. med. Wchnschr 78:1151-1155 (Nov. 27) 1948.

8. Crowe, H. W.: Trafuril as Treatment in Muscular Rheumatism: A Preliminary Report, Rheumatism 7:75-77 (Oct.) 1951.

9. Strehler, E., cited by Crowe, op. cit.

10. Nassim, J. R., and Banner, H.: Skin Response to Local Application of Nicotinic Acid Ester in Rheumatoid Arthritis; Preliminary Communication, Lancet 1:699, 1952.

11. Streitfeld, M. M., and Saslaw, M. S.: Unpublished data.

12. Waksman, B. H.: Etiology of Rheumatic Fever: A Review of Theories and Evidence, Medicine 28:143, 1949.

13. Stark-Mittleholzer, cited by Crowe, op. cit.

14. Gross, F., and Merz, E. ibid.

15. Brown, E. E., and Wasson, V. P.: Capillary Resistance in Rheumatic Children, J. Ped. 18:328, 1941.

16. Haydu, G. G.: Studies on the Pathogenesis of Rheumatoid Arthritis, Rheumatism 6:133-136 (July) 1950.

17. Shetlar, M. R.: Cortisone Treatment in Rheumatic Fever, J. Lab. & Clin. Med. 39:372-382 (March) 1952.

18. Abrahams, D. G.: Glynn, L. E., and Leowi, G.: Heparin Intolerance in Rheumatic Fever, Clin. Sc. 10:1-11 (Feb.) 1951.

19. Bywaters, E. G. L.: Aetiological Factors in Rheumatic Heart Disease, Brit. M. Bull. 8:343-348, 1952.

20. Meyer, Karl: The Biological Significance of Hyaluronic Acid and Hyaluronidase, Phys. Reviews 27:335 (July) 1947.

21. Kahn, L. and Goldring, D.: Present Day Concepts in the Etiology of Rheumatic Fever, J. Missouri State Med. Assn. 49:33, 1952.

22. Swift, H. F. in Dubos, R. J.: Bacterial and Mycotic Infections of Man, 2nd ed. Philadelphia, J. B. Lippincott Company, 1952, pp. 283-284.

23. Gregg, G. S., and Gregg, F. J.: Etiology of Rheumatic Fever, Penns. Med. J. 54:132-3 (Feb.) 1951.