PITUITARY CORTICOTROPHIN (ACTH) PRODUCTION IN RHEUMATOID ARTHRITIS TESTED INDIRECTLY WITH METOPIRON (Su 4885)

BY

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Metopiron [2-methyl-1,2-bis-3-pyridyl)-1-propa-none; Su 4885] inhibits 11- β -hydroxylation in the adrenal cortex, and this inhibition is reflected as an increased production of ACTH in the anterior pituitary. It was found by Liddle, Estep, Kendall, Williams, and Townes (1959) that the pituitary production of ACTH in man can be measured with aid of Metopiron and numerous clinical studies have since been carried out which have shown that the Metopiron test can be employed as a reliable indirect method of evaluating the pituitary production of ACTH (*e.g.* Andersson, 1961; Faber, 1961; Gold, Kent, and Forsham, 1961).

In this paper we report results that obtained when the Metopiron test was applied to patients with rheumatoid arthritis.

Material and Methods

Our rheumatoid group comprised ten patients (3 male, 7 female; average age 53.7 yrs) who had not received steroid treatment for one year before the experiment.

The control group also comprised ten patients (3 male, 7 female; average age 46.0 yrs); the diagnoses of these patients are shown in Table II.

The patients in both groups were hospitalized during the whole experimental period of 6 days. The first, second, fifth, and sixth days were control days when Metopiron was not administered. On the third and fourth days the patients were all given 500 mg. Metopiron orally every 6 hours.

The 24-hr urine was collected and analysed for total 17-hydroxycorticosteroids (17-OHCS) by a modification of the method of Jenkins, Forsham, Laidlaw, Reddy, and Thorn (1955).

Results

The results of the Metopiron tests for the rheumatoid and control groups are summarized in Tables I and II (opposite).

The differences between the mean values for the two groups are not statistically significant.

A tendency for a delayed reaction in the Metopiron test was evident in the rheumatoid group. The maximal average excretion of total 17-OHCS was recorded in the rheumatoid group on the fifth day (the day following the Metopiron administration) whereas it was recorded on the fourth day (the second day of Metopiron administration) in the control group.

Discussion

Our results seem to indicate that in rheumatoid patients the capacity of the pituitary to produce ACTH, as determined indirectly by the exogenous inhibition of 11- β -hydroxylation in the adrenal cortex, does not differ from the capacity in patients with various "non-collagenous" diseases. A tendency was noted in the rheumatoid patients for the response of the pituitary to be delayed, but it was not possible to determine on the basis of our results whether this finding was accidental or not. In an earlier study (Kalliomäki and Rauramo, 1960) it was found that urinary excretion of gonadotrophins is normal in female rheumatoid patients. Signs suggesting the thyrohypophyseal syndrome and an increased extracellular phase in rheumatoid arthritis (Kalliomäki and Holopainen, 1956; Kalliomäki, Kirpilä, Koskinen, and Laine, 1958) may reflect disturbances in the hypothalamo-pituitary system. It is possible that the delayed response of the anterior pituitary gland in the Metopiron test is also a manifestation of the same kind.

Metopiron has weak diuretic properties (it inhibits aldosterone production). Tables I and II show that the average total output of urine of the rheumatoid patients on the third, fourth, and fifth days was about half a litre larger than the average output in the control group. This may be taken as an indication of the above-mentioned predisposition to an increase in the extracellular fluid

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TABLE I
RESULTS OF METOPIRON TEST IN THE RHEUMATOID GROUP

Case No.	Sex	Age (yrs)	History of Rheumatoid Arthritis (yrs)	Stage of Rheumatoid Arthritis	Erythrocyte Sedimentation Rate (mm./hr)	Urinary Excretion of Total 17-OHCS (mg./24 hrs)					
						Days					
						Control		Metopiron		Control	
						1	2	3	4	5	6
1	M	44	30	III	100	19.2	12.6	12.8	6.8	16.0	9.8
2	M	33	5	III	60	1.8	3.4	9.1	5.8	2.6	3.4
3	M	52	27	III	84	2.0	6.2	5.4	6.5	2.4	3.7
4	F	38	1/4	III	117	5.9	2.1	8.4	9.2	13.9	2.0
5	F	63	1/3	II	74	8.4	5.6	9.5	12.0	7.6	3.7
6	F	69	8	III	43	2.5	4.6	9.2	6.4	8.4	2.4
7	F	55	8	IV	31	11.0	4.6	11.2	18.6	12.9	8.0
8	F	67	30	IV	50	4.8	1.3	8.8	5.8	11.8	6.9
9	F	19	10	IV	20	4.5	2.3	10.3	13.9	13.0	1.7
10	F	50	17	III	54	3.1	2.3	4.3	4.1	4.9	7.0
Mean Total 17-OHCS Excreted (mg./24 hrs)						6.3	4.3	8.9	8.9	9.4	4.9
Average Volume 24-hrs Urine (ml.)						1,080	990	1,415	1,105	1,210	925

TABLE II
RESULTS OF METOPIRON TEST IN THE CONTROL GROUP

Case No.	Sex	Age (yrs)	Diagnosis	Urinary Excretion of Total 17-OHCS (mg./24 hrs)					
				Days					
				Control		Metopiron		Control	
				1	2	3	4	5	6
1	M	64	Cardiac infarction	4.3	4.0	12.2	10.5	5.2	lacking
2	M	56	Cardiac infarction	3.2	1.8	2.1	1.4	0.8	lacking
3	M	43	Cardiac infarction	4.0	6.0	5.2	8.4	8.4	2.1
4	F	54	"Little stroke"	13.5	5.9	13.2	19.7	13.5	4.5
5	F	62	Peptic ulcer	7.2	7.2	8.1	6.9	6.7	4.6
6	F	52	Angina pectoris	3.4	1.4	4.4	7.2	3.2	1.4
7	F	47	Acute infection	8.2	5.8	8.6	7.2	5.6	5.4
8	F	34	Hypochromic anaemia	6.0	4.3	4.2	9.7	3.8	lacking
9	F	66	Pleural carcinosis	12.0	13.9	17.3	14.0	20.0	10.0
10	F	59	Hodgkin's disease	4.1	5.0	9.2	13.6	13.8	10.4
Mean Total 17-OHCS Excreted (mg./24 hrs)				6.6	5.5	8.5	9.9	8.1	5.5
Average Volume 24-hrs Urine (ml.)				1,185	840	1,238	1,095	1,000]	920

phase and to increased oedema in rheumatoid arthritis.

Summary

The variation of the production of ACTH by the pituitary gland when 11- β -hydroxylation in the adrenal cortex is inhibited by Metopiron ("Su4885") has been followed by determining the mean daily excretion of total 17-hydroxycorticosteroids in ten patients with rheumatoid arthritis and in ten control patients with various internal diseases.

The response of the pituitary gland did not differ essentially in the rheumatoid and control groups, although a tendency for the response to be delayed was noted in the patients with rheumatoid arthritis.

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Production de corticotrophine (ACTH) dans l'arthrite rhumatoïdale sous l'influence indirecte de Metopiron (Su 4885)**RÉSUMÉ**

On étudia les variations dans la formation d'ACTH par l'hypophyse après l'inhibition de l'hydroxylation en position 11-B dans l'écorce surrénale par Metopiron (Su 4885), en déterminant l'élimination moyenne totale par jour des 17-hydroxycorticostéroïdes chez dix malades atteints d'arthrite rhumatoïdale et dix témoins souffrant de diverses autres maladies.

La réponse hypophysaire ne révéla pas de différence essentielle entre le groupe rhumatismal et le groupe témoin, mais chez les malades atteints d'arthrite rhumatoïdale on nota une tendance à répondre tardivement.

Producción de corticotrofina hipofisaria (ACTH) suscitada indirectamente en artritis reumatoide con Metopiron (Su 4885)**SUMARIO**

Se estudiaron las variaciones en la producción de ACTH por la hipófisis, después de inhibir la 11-B hidroxilación en la corteza suprarrenal con Metopiron (Su 4885), determinando la eliminación media diaria de 17-hidroxocorticosteroides en diez enfermos con artritis reumatoide y en diez testigos padeciendo de diversas otras enfermedades.

La respuesta hipofisaria no presentó ninguna diferencia esencial entre el grupo con artritis reumatoide y el de control, aunque en los enfermos con artritis reumatoide se notó tendencia a respuestas retardadas.