Amopyroquin (Propoquin) in Rheumatoid Arthritis

By LEE E. BARTHOLOMEW AND IVAN F. DUFF

A controlled, double-blind trial of amopyroquin *vs.* placebo has been completed in 15 patients with active, classical or definite rheumatoid arthritis.

Improvement in all the parameters determined occurred while the patients were on amopyroquin. Grip strength, sedimentation rate, and Lansbury's indices showed statistically significant improvement while on amopyroquin. Improvement in the 50-foot walk and A.R.A. functional capacity approached statistical significance.

Amopyroquin was well tolerated, but asymptomatic elevation of SGOT occurred in four patients and appeared to be related to the drug. Other tests of liver function remained normal.

Un controlate essayo a duple anonymato esseva effectuate con amopyroquina contra placebo in un gruppo de 15 patientes con active arthritis rheumatoide classic o definite.

Melioration in omne le parametros studiate occurreva durante que le patientes recipeva amopyroquina. Fortia del sasir, sedimentation erythrocytic, e le indices de Lansbury indicava statisticamente significative meliorationes durante le curso de amopyroquina. Melioration in le ambulation de 50 pedes e *in le capacitate functional secundo le* A.R.A. approchava un grado de signification statistic.

Amopyroquina esseva ben tolerate, sed un elevation asymptomatic de transaminase glutamic-oxaloacetic del sero occurreva in quatro patientes, apparentemente in relation con le pharmaco. Altere tests del function hepatic remaneva normal.

VARIOUS SYNTHETIC antimalarial preparations of the 4-amino-quinolone group have been used in the treatment of rheumatoid arthritis with encouraging results. A number of well controlled, double-blind studies using chloroquine and hydroxychloroquine have shown that both of these drugs have anti-rheumatic properties of moderate degree.[1-7]

Early reports of the use of amodiaquin (Camoquin) in rheumatoid arthritis were also encouraging; but gastrointestinal, neurologic, hepatic, and hematologic manifestations were serious enough to limit its usefulness.[8-10] Similar side effects have been reported in the treatment of discoid and systemic lupus erythematosus with amodiaquin.[11-14] Amopyroquin (Propoquin) is a close analogue of amodiaquin (fig. 1). Preliminary studies in animals[15] and man indicated good tolerance, low toxicity, and effective antimalarial properties. We, therefore, undertook a preliminary clinical trial to determine the antirheumatic properties and the toxicity of amopyroquin in patients with rheumatoid arthritis. Classical double-blind, cross-over technics were used to compare amopyroquin with placebo.

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The Rackham Arthritis Research Unit is supported by a grant from the Horace H. Rackham School of Graduate Studies.

Presented in part at the annual meeting of the American Rheumatism Association, June 21 and 22, 1962 in Chicago, Ill.

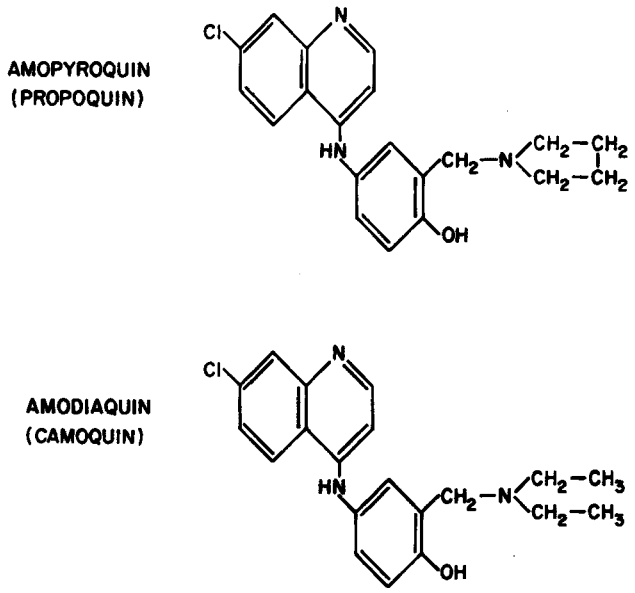

Fig. 1

Materials and Methods

Fifteen adult patients with active, classical or definite rheumatoid arthritis were selected. Active disease had been present for at least 1 year, and all patients had at least five clinically active joints at the outset of the study. None had ever received antimalarial drugs in the past. Systemic steroids had not been used for at least 3 months, although intra-articular steroids were used in a few cases during the study. Single joints were injected in three patients while on placebo, and in one patient while on amopyroquin. Patients receiving maintenance crysotherapy were acceptable if more than 1.5 Gm. had been given, and if their disease was stable and active (two cases). Gold was discontinued when the study was started. All patients were on salicylates and home physical therapy programs. These were continued. At the beginning of the study, patients were instructed in the *ad lib.* use of salicylates. Many, however, tended to continue on their previous dosage despite improvement.

The study was of 10 months' duration: 5 months on amopyroquin (Propoquin*), 150 mg. per day in a single capsule with breakfast, and 5 months on a matching placebo. Patients were placed into Group A (amopyroquin first) or Group B (placebo first) by random allocation. No one involved in the study was aware of which preparation was being given. Patients were seen 14 times during the study; twice before therapy, and at 4-week intervals during therapy. An additional visit occured 2 weeks after the start of each treatment period in order to note any early side effects. All patients were ambulatory and were seen in the Rackham Arthritis Research Unit. As far as possible, patients were seen by the same observer on each visit.

At each visit histories were obtained, and the following items recorded: consistency of drug ingestion, average aspirin dosage, other medications, general well-being, and A.R.A. functional capacity. Specific questions concerning possible drug toxicity were likewise recorded.

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*Propoquin (amopyroquin) and matching placebo were supplied by Dr. P. F. Robert de Caries; Parke, Davis & Co.

Table 1.—*Patient Characteristics at Beginning of Study*

	Group A	Group B
No. patients	8	7
Males	1	1
Females	7	6
Mean age (years)	47	58
Range	28–62	42–67
Duration of disease (years)	3.4 (1.5–7)	5.4 (1–14)
Positive latex test	5	5
Rheumatoid nodules	2	4
Stage of R.A.		
I	3	1
II	3	4
III	2	2
Functional capacity		
II	6	4
III	2	3

Group A: received amopyroquin first 5 months.
Group B: received placebo first 5 months.

Hemoglobin, leukocyte count, Westergren sedimentation rate, complete urinalysis, blood urea nitrogen, and serum glutamic-oxaloacetic transaminase (SGOT) values were obtained at each visit.

Grip strength was determined using a small type, English-designed cuff* and inflating to 20 mm. Hg. The three readings of each hand were averaged. The time to walk 50 feet as fast as possible without running was recorded with a stop-watch. The number and location of subcutaneous rheumatoid nodules were noted on each visit.

Complete physical examinations were performed every 2 months. Weight was recorded on each visit. The following were obtained at the first, middle, and final visits: x-rays of the hands and wrists, and one other joint (if more active or involved than the hands or wrists); latex fixation test to the final dilution; total serum proteins; and serum protein paper electrophoresis.

The following articular indices were recorded: (1) Tenderness on pressure and/or pain on passive motion—a value of one for each joint and half values for doubtful tenderness. (2) Joint swelling evaluated on a 0–4 plus scale for each joint. Total numerical values were given for both joint tenderness and swelling for each visit. In addition, Lansbury's articular and systemic indices were calculated for each visit.[16] The latter were determined without values for fatigue.

Methods of Analysis

Table 1 shows the composition of the two groups. They were approximately comparable in most respects except that the mean age of Group A (receiving amopyroquin first) was younger and the mean duration of disease was somewhat shorter.

Two types of comparisons were made: (1) A cross-over comparison with each patient serving as his own control. Pre-treatment values in Groups A and B were compared with those at the end of 5 months, and in turn the 5-month values were compared with those obtained at the end of the 10-month period. (2) Groups A and B were compared for the first 5-month period only, with Group A on amopyroquin and Group B on placebo.

The statistical analyses were performed by Ronald R. Gauch, Department of Clinical Investigation, Parke, Davis & Co., Ann Arbor, Mich. The Mann Whitney U Test was used for the comparisons between Groups A and B for the first 5-month period. The Wilcoxon

*Supplied by Dr. Donald Mainland, New York University Medical Center.

Table 2.—*Group A (Amopyroquin-Placebo): Mean Values and Per Cent Change—Eight Cases*

	Pretreatment Mean	After 5 Months Placebo		After 5 Months Amopyroquin	
		Mean	% Change*	Mean	% Change*
Morning stiffness (hours)	2.72	1.76	+35	1.52	+13
Number of tender joints	28	21	+25	18	+14
Joint swelling†	23.5	21	+11	20	+5
50-foot walk (sec.)	11.6	10.1	+13	10.0	+1
Grip strength (mm. Hg)	140	171	+22	152	−10
Hemoglobin (Gm. %)	12.2	13.0	+6	12.7	−2
ESR (mm./hr.)	43	34	+21	46	−35
A.R.A. functional capacity	2.1	1.8	+15	1.9	−9
Articular index‡	105	68	+35	70	−3
Systemic index‡	76	58	+24	62	−7

*+ indicates improvement; − deterioration.
†Total joint swelling, each joint graded 0–4.
‡Lansbury's indices.

Test was used for the cross-over comparisons. The p values were obtained for each of the groups, and values less than 0.05 were considered significant.

Results

Of the 15 patients started on the study, one dropped out at the end of 5 months on placebo. In three patients, the drug was stopped for periods up to 7 weeks because of SGOT elevation. These patients, as well as one hospitalized for 3 weeks for congestive heart failure, are included in the analysis.

Patients in Group A (table 2) showed mean improvement in all indices after 5 months of amopyroquin. This improvement appeared to be maintained for the next 5 months on placebo in some indices (morning stiffness, joint tenderness, Lansbury's indices, and the 50-foot walk), but not in grip strength and sedimentation rate.

The patients in Group B (table 3) showed improvement in morning stiffness and joint tenderness, but no change or deterioration in all other indices during the first period on placebo. When switched to amopyroquin, again improvement was seen in all indices.

Statistically, none of the patients showed significant improvement while on placebo. In both groups significant improvement was found for some indices while on amopyroquin. Grip strength, sedimentation rate and Lansbury's systemic index had p values of less than 0.05. The p values for the 50-foot walk, functional capacity, and articular index did approach 0.05.

Table 4 compares the first 5-month period of each group. It is to be noted that Group B (placebo) has seven cases—one dropped out at the end of the first period. Improvement occurred in all indices in patients receiving amopyroquin, but only Lansbury's articular index was significant ($p = 0.03$). However, the sedimentation rate and systemic index approached statistical significance. In the placebo group, only morning stiffness and total tender joints showed improvement. These were not statistically significant.

Comparing Groups A and B for the first 5-month period, the latex titer fell

Table 3.—*Group B (Placebo-Amopyroquin): Mean Values and Per Cent Change—Six Cases*

	Pretreatment Mean	After 5 Months Amopyroquin		After 5 Months Placebo	
		Mean	% Change*	Mean	% Change*
Morning stiffness (hours)	2.00	1.46	+27	.76	+48
Number of tender joints	31.8	26	+17	17	+35
Joint swelling†	24	24	0	14	+41
50-foot walk (sec.)	11.8	16.8	−51	9.3	+45
Grip strength (mm. Hg)	123	126	+3	181	+44
Hemoglobin (Gm. %)	12.9	12.9	0	13.5	+5
ESR (mm./hr.)	47	52	−11	36	+31
A.R.A. functional capacity	2.2	2.2	0	1.5	+32
Articular index‡	120	107	+10	71	+33
Systemic index‡	67	63	+6	43	+32

*+ indicates improvement; − deterioration.
†Total joint swelling, each joint graded 0–4.
‡Lansbury's indices.

in four of the five latex positive patients on amopyroquin, and in two of the five positive patients on placebo. When switched to amopyroquin, the remaining three patients in the latter group showed a fall in titer. The decrease in titer was of two tube dilutions or more in seven cases, and one tube dilution in two cases.

Subcutaneouus nodules disappeared or were decreased in number in three patients on amopyroquin, and in one on placebo .

There was very little change in the gamma globulin values with amopyroquin, but a definite increase in serum albumin occurred. Serum albumin decreased in all except one patient while on placebo.

No appreciable weight change occurred on amopyroquin. There was a mean loss of ¼ lb. (−8 to +11 lb.). On placebo, the mean weight change was minus 2½ lb. (−15 to +10 lb.).

The x-rays revealed very little change during the 10-month period. Erosions increased slightly in two patients on placebo, and two on amopyroquin. There appeared to be slight improvement in one case while on amopyroquin.

Toxicity

Amopyroquin was not stopped in any patient because of untoward symptoms or abnormal physical findings. Symptoms suggestive of toxicity were more frequent in patients on placebo, particularly anorexia, abdominal distress, headaches, and edema. Nausea, vomiting, or diarrhea were not seen while on amopyroquin. Skin rash and pruritus likewise were not associated with the active preparation. Transient blurred vision was noted in two patients on placebo and one on amopyroquin. These patients and several others had slit lamp examinations after the study, and no abnormalities were encountered.

A transient lowering of the leukocyte count occurred in three patients on amopyroquin to levels of 4000–4500 cells/cu. mm. There was essentially no change in values for blood urea nitrogen or complete urinalyses.

Table 4.—*Comparison of Mean Values and Per Cent Change of Eight Cases Started on Amopyroquin with Seven Cases Started on Placebo*

	Pretreatment Mean	After 5 Months Amopyroquin		Pretreatment Mean	After 5 Months Placebo	
		Mean	% Change*		Mean	% Change*
Morning stiffness (hours)	2.72	1.76	+35	2.12	1.68	+21
Number of tender joints	28	21	+25	31.6	28	+11
Joint swelling†	23.5	21	+11	24.8	24.8	0
50-foot walk (sec.)	11.6	10.1	+13	12.6	17.7	−41
Grip strength (mm. Hg)	140	171	+22	122	123	0
Hemoglobin (Gm. %)	12.2	13.0	+6	12.9	12.8	−1
ESR (mm./hr.)	43	34	+21	53	57	−7
A.R.A. functional capacity	2.1	1.8	+14	2.2	2.2	0
Articular index‡	105	68	+35	117	115	+2
Systemic index‡	76	58	+24	71	67	+5

*+ indicates improvement; − deterioration.
†Total joint swelling, each joint graded 0–4.
‡Lansbury's indices.

In four patients definite elevation of SGOT occurred while taking amopyroquin. The highest values for each patient ranged from 106 to 440 units (normal 15–40 units). One patient was a 72-year-old lady who developed mild congestive heart failure. Left bundle branch was found on her electrocardiogram. She was continued on amopyroquin; and the SGOT values fell from 106 units at 3 months of therapy to 77 units at the end of 5 months of therapy. Two weeks after switching to placebo the SGOT became normal.

The other three patients were asymptomatic. Elevated SGOT levels were first noted after 1 to 2 months of treatment. The drug was stopped in each instance for 4 to 7 weeks, at which time the SGOT had significantly dropped. In each case it was restarted. In one patient the values gradually fell to normal while continuing amopyroquin. In the other two cases the values again became elevated, but not as high as originally.

Serum bilirubin, bromosulfalein excretion, and alkaline phosphatase tests remained normal. Two patients had positive cephalin flocculation tests, but pretreatment values were not available. None of the patients developed hepatosplenomegaly or liver tenderness.

Discussion

The purpose of this study was to determine whether or not amopyroquin has anti-rheumatic properties, and how toxic the drug might be in patients with rheumatoid arthritis. Patients with both mild and early, and severe and late rheumatoid arthritis were selected. The cross-over, double-blind technic seemed the most suitable method for study. Treating the data in

a cross-over trial is always subject to some bias, since the preparation given initially has a better chance of causing improvement than the preparation given during the second half of the trial. However, three patients who developed elevated SGOT levels were taken off amopyroquin for periods of 4 to 7 weeks. They are included in the evaluation, and this would tend to decrease the apparent effectiveness of the drug. Nevertheless, amopyroquin appears to have definite, but moderate anti-rheumatic properties.

The results, as shown, compare only the initial and final values for each period. The various indices were determined six times for each 5-month period. When improvement occurred with amopyroquin, it was gradual and usually was seen first at the end of 4 weeks. A definite carry-over effect occurred in Group A (amopyroquin first) which lasted 2 to 4 months or longer during the placebo period.

Amopyroquin was very well tolerated in this group of patients. This is somewhat surprising since amodiaquin caused side effects in a high proportion of patients. The significance of the elevated SGOT levels is yet to be determined. Presumably, this represents liver transaminase, though there was no other evidence of liver involvement. We have not eliminated other sources of transaminase release. The presence of amopyroquin itself in serum does not interfere with the colorimetric method[17] of determining SGOT as used in our hospital.[18] Bepler et al.[8] reported serum transaminase elevation up to 100 units in four patients treated with amodiaquin.

The dosage of amopyroquin (150 mg./day) was arbitrarily chosen on the basis of results in preclinical and early clinical trials. Perhaps higher or lower doses could be used to advantage.

This study again demonstrates the sensitivity of Lansbury's indices. In addition to Lansbury's indices, sedimentation rate and grip strength individually were good indicators of disease activity.

Summary

A controlled, double-blind trial of amopyroquin *vs.* placebo has been completed in a group of 15 patients with classical or definite rheumatoid arthritis.

Improvement occurred while on amopyroquin in the various indices recorded, with statistical significance noted in Lansbury's indices, grip strength and sedimentation rate.

Amopyroquin was well tolerated, but elevation of SGOT occurred in four of the patients.

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