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Monitoring serum gold values to improve chrysotherapy in rheumatoid arthritis

A. LORBER, C. J. ATKINS, C. C. CHANG, Y. B. LEE, J. STARRS, AND R. A. BOVY

From the University of Southern California School of Medicine, Department of Medicine, Rheumatic Disease and Immunology Section, Los Angeles, California, and the Veterans Administration Hospital, Long Beach, California

Forestier (1929) first used gold salts to treat rheumatoid arthritis (RA), and controlled studies (*e.g.* Empire Rheumatism Council, 1960, 1961) later confirmed their effectiveness. An empirical schedule of treatment (conventional chrysotherapy) evolved, using 50 mg. monthly, but this might be further improved if dosage could be adjusted for each patient according to the serum level of gold. Atomic absorption spectrophotometric analysis now makes practicable the repeated estimation of gold in serum and urine, offering a considerable advantage over the methods used by previous authors (Goodwin, 1954; Smith, Peak, Kron, Hermann, Deltoro, and Goldman, 1958; Freyberg, Block,and Levey, 1941).

We report below the results of a comparison of the effectiveness of fixed-dose conventional chrysotherapy with a dosage varied according to the concentration of gold in the serum of the individual patient.

Material and methods

CRITERIA FOR ADMISSION TO THE TRIAL

Patients meeting the criteria of the American Rheumatism Association for a diagnosis of definite or classical active polyarticular rheumatoid arthritis were admitted and all anti-rheumatic medication other than salicylates was terminated or reduced to minimal maintenance levels. The clinical characteristics of the nineteen women and four men included in the study are detailed in Table I. With the exception of the first five patients listed in Table I who had previously received chrysotherapy, they were assigned on a random basis (Fisher and Yates, 1938) to the conventional or adjusted therapy regimen.

DESIGN OF GOLD THERAPY

The control group C received 100–1,200 mg. sodium auro-thiomalate (Merck, Sharpe, and Dohme) by intramuscular injection of 50 mg./week for 20 to 24 weeks. Thereafter, 50 mg. were given monthly followed by three weekly placebo injections (Tables I and II). The adjusted therapy group A also received a series of 20 to 24 injections of 50 mg. gold thiomalate. The dosage was then adjusted (usually to 75 mg.) to maintain a blood concentration of 300 μg. per cent. as determined by measuring the gold in the previous week's blood specimen. To eliminate the possibility of a differential response to the frequency of injections, all patients received weekly injections of either placebo (physiological saline) or gold as indicated. The first five patients listed in Table I designated as Group A* had been receiving gold therapy on a conventional dosage regimen when admitted to the study and thus are not included in the clinical comparison. These patients are, however, included in the study as their gold serum levels have been maintained above 300–400 μg./per cent. by the adjusted regimen for more than 4 years and thus represent the longest test periods available.

TESTING PROCEDURES AND MEASUREMENTS

At each patient's weekly examination, a complete blood count (CBC), serum gold levels, and urine analysis were determined. Every 20 weeks, a complete physical examination was made, including the subjective and objective response to treatment (Lansbury, 1966). A physiotherapist who was unaware of the dosages given recorded the range of joint motion including 28 variables (Heck, Hendryson, and Rowe, 1965). The patients were hospitalized* for 7 days at the 10th, 20th, and 60th week (and every 30 weeks thereafter) from the start of therapy for collection and daily quantitation of gold content in serum, urine, and (in some subjects) stool specimen. Comprehensive laboratory studies were conducted every 20 weeks to detect toxic or adverse reactions affecting haemopoietic, hepatic, or renal function; these included creatinine clearance, 24-hr protein excretion, and renal tubular concentration function.

Serum, urine, and faecal gold determinations were performed by atomic absorption spectroscopy, using an internal standard (Lorber, Cohen, Chang, and Anderson, 1968).

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Requests for reprints: A. Lorber, M.D., Veterans Administration Hospital, Ward G3, 5901 East Seventh St., Long Beach, California 90801, U.S.A.

Table I *Clinical particulars of 23 patients in order of admission to the trial*

Patient no.	*Date admitted*	*Group*	*Age (yrs.)*	*Sex*	*Race*	*Duration of disease (yrs.)*	*RF titre*	*Anti-DNP*	*LE Prep*	*Nodules*	*Erosions*	*Functional index*
1	Mar. '67	A*	39	F	W	3	—	−	−	−	+	III
2	Apr. '67	A*	49	F	N	3·5	1,280	−	−	−	+	III
3	May '67	A*	51	F	W	10	320	−	−	−	+	II
4	Jun. '67	A*	61	F	O	8	5,120	−	−	−	+	III
5	Apr. '68	A*	42	F	W	1	2,560	−	−	+	+	III
6	Aug. '68	A	29	F	N	6	2,560	−	−	−	+	III
7	Aug. '68	A	68	M	N	3	320	−	−	−	+	III
8	Oct. '68	C	45	F	N	3	5,120	+	−	−	+	IV
9	Oct. '68	C	39	F	W	4	640	+	−	−	+	II
10	Nov. '68	A	31	F	W	11	2,560	+	−	−	+	II
11	Nov. '68	A	47	F	W	2	1,280	+	−	−	+	II
12	Nov. '68	C	48	F	N	20	2,560	−	−	−	+	III
13	Dec. '68	C	57	M	N	<1	10,240	−	−	−	+	II
14	Jan. '69	C	46	M	W	3	5,120	−	−	−	−	II
15	Jan. '69	C	47	F	W	4	1,280	−	−	+	+	III
16	Feb. '69	A	38	F	N	3	2,560	−	−	−	+	III
17	Apr. '69	C	51	F	W	18	5,120	−	−	+	+	III
18	Apr. '69	C	44	F	W	1	640	−	−	−	+	III
19	Apr. '69	A	29	F	W	5	20,480	+	3+	+	+	III
20	May '69	A	66	F	W	2	5,120	−	2+	+	+	III
21	Jun. '69	A	57	F	W	19	5,120	−	1+	+	+	III
22	Sept. '69	A	31	F	N	2	10,240	−	−	−	+	II
23	Oct. '69	C	40	M	W	3	1,280	+	−	−	+	II

A = Adjusted
C = Conventional
* Received crysotherapy before adjusted regimen.
+ = Positive
− = Negative
W = Caucasian
N = Negro
O = Oriental
RF titres are expressed as reciprocal of dilution.

Results

During the first 20-week period of therapy, approximately half of the subjects failed to achieve the specified level of >300 μg. per cent. (Fig. 1). For those patients scheduled to receive the adjusted therapy, the dosage was subsequently increased and continued at weekly intervals as needed. Approximately 10 per cent. of the patients showed serum gold values exceeding the specified range during the initial 20-weeks and for them the dosage was omitted as necessary to maintain the desired range. Therapy for the control group was continued at an average dose of 56 mg. gold thiomalate/month compared with 183 mg./month for the adjusted group (Fig. 2; Table II). After the gold injection, a sharp increase in serum gold levels attains a maximum within 12 hours and falls gradually throughout the week. Thus, in the adjusted regimen, such peaks are attained three times more frequently than in patients treated under conventional monthly injection schedules. (Fig. 3, overleaf).

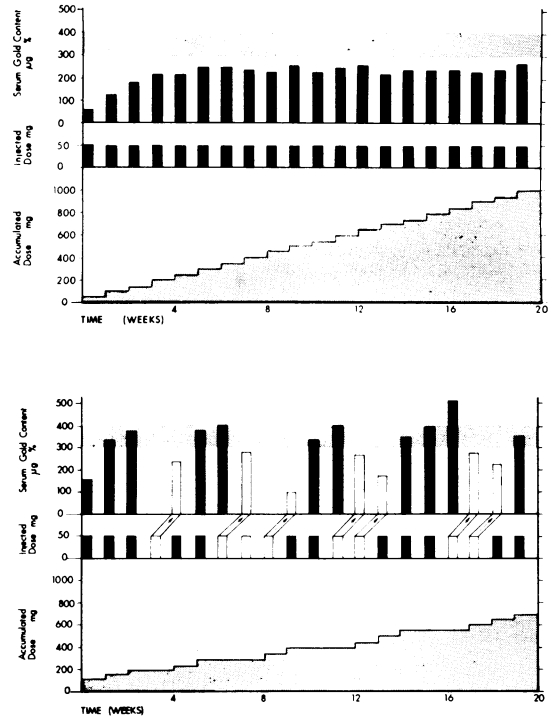

FIG. 1 *Individual response by serum gold values to sequential 50-mg. injections of gold sodium thiomalate. Shaded band represents minimum serum gold level to be maintained.*

(A) Specified range not attained in Patient 6. Additional weekly gold injections of 50–75 mg. were required for the succeeding 40 weeks (see Table II).

(B) Patient 21 shows a much higher response during the initial period of chrysotherapy. For this reason, dosage was omitted at the fourth scheduled gold injection, and at subsequent times indicated by diagonal arrows. Excessively high serum gold levels would probably have resulted had the patient received weekly gold injections according to the conventional schedule. A striking clinical response was noted within 6 weeks of starting chrysotherapy in contrast to Patient 6

Table II *Comparison of weekly serum gold levels in patients† receiving different chrysotherapy regimens (21–60 week period)*

Therapy	*Conventional*						*Adjusted*					
Patient no.	8		9		12		6		16		21	
Week of therapy	*Serum level*	*Dose (mg.)*	*Serum level*	*Dose (mg.)*	*Serum level*	*Dose (mg.)*	*Serum level*	*Dose (mg.)*	*Serum level*	*Dose (mg.)*	*Serum level*	*Dose (mg.)*
21	308	*	340	*	164	*	265	50	335	50	455	*
22	185	*	198	*	76	*	216	50	F.A.	—	298	50
23	F.A.	—	163	*	68	*	239	50	308	50	403	25
24	93	50	140	50	55	50	228	50	330	50	363	*
25	190	*	255	*	152	50	190	50	404	50	235	50
26	115	*	183	*	192	*	220	50	528	*	368	50
27	78	*	100	*	155	*	263	50	354	*	465	*
28	75	50	135	50	93	*	258	50	252	50	273	25
29	170	*	229	*	85	50	243	50	F.A.	—	F.A.	*
30	138	*	133	*	190	*	253	50	F.A.	—	203	50
31	113	*	93	*	110	50	273	50	183	50	340	25
32	78	50	82	50	210	50	258	50	248	50	470	25
33	185	*	245	*	233	*	200	50	330	50	F.A.	*
34	115	*	133	*	158	*	220	50	385	*	F.A.	*
35	100	*	115	*	93	*	185	62·5	305	50	155	50
36	100	50	75	50	88	50	258	62·5	315	50	358	25
37	135	*	237	*	205	*	213	62·5	N.S.	50	408	50
38	110	*	135	*	128	*	280	62·5	350	50	418	*
39	63	50	114	*	103	*	285	75	399	*	F.A.	*
40	F.A.	—	91	50	73	50	345	75	345	*	Holiday	*
41	F.A.	—	276	*	175	*	293	75	250	50	145	50
42	72	*	168	*	100	*	338	50	318	50	333	50
43	65	50	118	*	88	*	398	50	343	50	413	25
44	159	*	110	50	78	50	268	50	F.A.	—	366	*
45	145	*	228	*	168	*	300	75	247	50	250	50
46	89	*	156	*	90	*	280	75	255	50	368	50
47	57	50	145	*	103	*	218	75	358	50	448	50
48	153	*	123	50	80	50	260	75	400	50	F.A.	*
49	120	*	283	*	208	*	280	75	455	*	315	25
50	78	*	213	*	111	*	323	75	295	*	315	25
51	66	50	160	*	83	*	388	50	220	50	324	25
52	178	*	145	50	100	50	321	50	280	50	326	25
53	123	*	275	*	160	*	366	75	375	50	338	25
64	98	*	195	*	130	*	364	50	365	*	F.A.	*
55	100	50	145	*	93	*	330	50	285	50	249	50
56	205	*	110	50	68	50	335	50	370	50	378	50
57	175	*	267	50	183	*	300	50	F.A.	—	460	25
58	108	*	F.A.	—	111	*	348	50	213	50	461	25
59	88	50	225	*	80	*	380	50	F.A.	—	390	*
60	195	*	143	*	68	50	375	50	223	50	293	50

* Placebo or no gold.
F.A. = Failed appointment or clinic cancelled. N.S. = No specimen.
† To conserve space, the tabulation for each group has been limited to three patients.

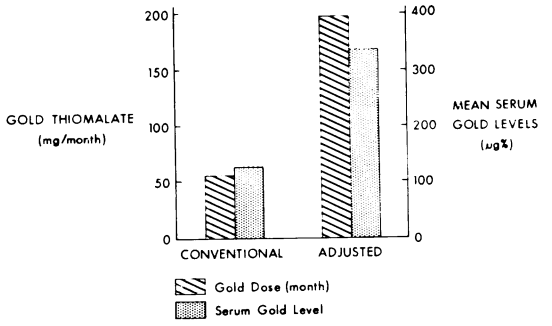

FIG. 2 *Relationship between dosage and resulting serum gold level beyond the 20th week of treatment for the two patient groups (conventional v. adjusted chrysotherapy)*

Renal gold excretion approximated 35 per cent. of the weekly administered dose during the first 20-week period of therapy (Fig. 4, overleaf). Excretion then increased to approximately 45 per cent. of the dose for the adjusted therapy group and declined to 20 per cent. of the dose for the control group. With occasional exceptions, faecal gold excretion constitutes only approximately 5 per cent. of the administered dose. The faecal excretion for patients receiving adjusted therapy was greater than for the controls.

ADVERSE REACTIONS (Table III, overleaf)
In no instance was the percentage of adverse reactions greater in the test group than in the control group.

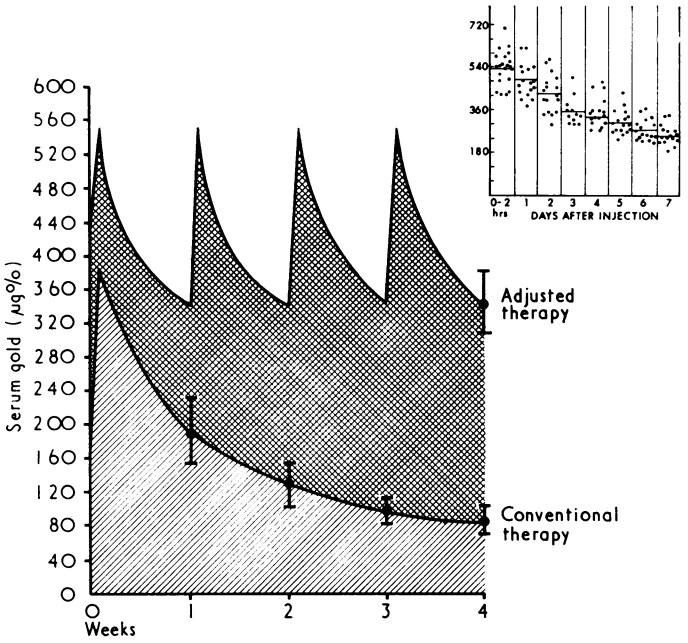

FIG. 3 *Comparison of serum gold levels (beyond 20th week of treatment) in patients receiving conventional chrysotherapy (monthly gold injections) with those achieved by the adjusted regimen (weekly gold injections). [See inset Figure]. A sharp increase exceeding 500 μg. per cent. is seen within 2 hours after injection. Thereafter, there is a progressive fall during the ensuing week(s). The differences in frequency and dosage of gold administration for the two groups are reflected in the ambient gold levels. The tissue distribution of gold and binding to immune reactants is increased whenever the serum gold concentration exceeds 300 μg. per cent*

Table III *Incidence of adverse reactions**

Therapy	*Conventional*		*Adjusted*	
No. of patients	10		16	
	No.	*Per cent.*	*No.*	*Per cent.*
Cutaneous				
Dermatitis	4	40	6	38
Exfoliation	0	0	0	0
Renal				
Haematuria	5	50	5	31
Proteinuria	1†	10	1‡	6
Haematopoietic				
Leucopenia§	1	10	1	6
Thrombocytopenia	0	0	0	0
Eosinophilia	4	40	4	25

* All patients observed for a minimum period of 60 weeks.
† 1+ proteinuria, transient recurrent.
‡ Renal biopsy disclosed wire loop changes of renal SLE.
§ No evidence of toxicity or bone marrow depression was noted on microscopic examination.

With regard to cutaneous reactions, the frequency of dermatitis attributed to gold was approximately 40 per cent. for both groups and was associated with eosinophilia in eight subjects; the latter preceded the rash in five subjects. In only two patients were the serum gold levels greater than 400 μg. per cent. at the onset of the rash. Apart from the eosinophilia, there was no irregularity in the differential white cell count. On one occasion, however, the latter constituted up to 33 per cent. of the differential count. With regard to an occasional report of microscopic haematuria (3 to 5 RBCs per high-power field), the highest serum gold level in association with the onset of the rash was 408 μg. per cent. Chrysotherapy was temporarily interrupted to conduct further studies, the results of which suggested that causes other than gold toxicity were responsible. No abnormality in hepatic or renal function was observed (Table IV).

COMPARISON OF EFFICACY

For each of eighteen patients 35 variables were recorded. Evaluation parameters included range of joint motion (28 variables), manual grip strength, erythrocyte sedimentation rate (Wintrobe), rheumatoid factor titre, Steinbrocker functional index (Steinbrocker, Traeger, and Batterman, 1949), and duration of morning stiffness. Patients included in this comparative study had not received chrysotherapy before admission to the study. Each group composed of nine patients manifested an approximately equal extent of improvement at the 20th week. Since divergence in dosage administration occurred primarily during the 20th to 60th weeks (Table II; Fig. 2), this interval was selected for comparison of the clinical response (Table V). The Kruskal Wallis one-way analysis of variance was applied for comparing the clinical response of the two therapy regimens. Statistical analysis indicated that patients who were receiving adjusted dosage therapy were significantly improved with regard to range of motion, grip strength, erythrocyte sedimentation rate, and decline in RF titre. Morning stiffness and the Steinbrocker functional index did not show a statistically significant difference between the two groups, though there was a tendency to a better rate of improvement with the adjusted therapy regimen.

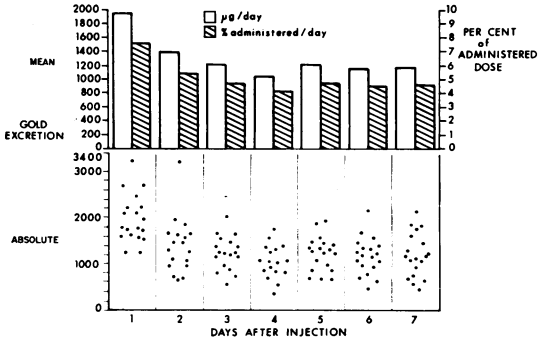

FIG. 4 *Variation in individual urinary gold excretion indicated on scattergram. Each point represents the absolute daily urinary gold excretion per patient observed at the 20th week of therapy. The highest gold excretion is noted within 24 hours after injection. The open bars above show the mean daily gold excretion for this group. The striped bars show the daily percentage excretion of the weekly administered gold dosage. A consistent relationship between serum gold values and urinary gold excretion was not observed*

Discussion

The data presented indicate that gold dosage can be safely adjusted on the basis of serum gold values to exceed 300 μg. per cent. to achieve positive clinical results. Basing the administered dosage on the amount of gold excreted in the urine as suggested by Smith and others, (1958) may be hazardous, as our results indicate that most of the administered gold was not recovered in urine or stool. In our experience, basing replacement therapy on levels of serum gold allows weekly administration of gold salts in higher dosage and for longer periods of time than has previously been reported. Serious adverse reactions were not encountered despite the sustained high levels. The frequent association of eosinophilia with dermatitis is suggestive of hypersensitivity rather than of gold toxicity. It is our impression that dermatitis was aggravated by wide fluctuations in serum gold content, thus supporting the concept of maintaining more constant levels.

From a theoretical standpoint, the higher sustained blood gold levels may exert a beneficial effect *via* one of several mechanisms. Transport of gold from blood to tissues, *i.e*, to the synovial fluid, should be enhanced. Higher tissue gold levels may facilitate the inhibition of acid hydrolases (Persellin and Ziff, 1966; Ennis, Granda, and Posner, 1968).

The distribution of gold to the various serum protein fractions also seems to be influenced by the serum gold concentrations. At levels achieved with conventional chrysotherapy, gold binds principally to serum albumin (McQueen and Dykes, 1969; Lawrence, 1961); at higher values, however, we have observed proportional binding of gold to immunoglobulins and complement (Lorber, Bovy, and Chang, 1972) (Fig. 3, opposite). Therefore, it may be possible, by regulating serum gold values, to increase the binding of gold to protein reactants involved in the formation of immune complexes which may then gain access to those cells engaged in phagocytosis of these complexes.

With regard to the efficacy of the programme, in view of the relatively small number of participants, no definitive conclusion should yet be drawn. It is nevertheless possible, on the basis of our observations, to make some generalizations regarding the relationships between clinical response and serum gold levels:

(1) Patients noted to have high serum gold levels early during therapy are more likely to manifest an early improvement, *i.e.* before 20 weeks.

(2) Conversely, patients who did not achieve the specified serum gold levels generally did not fare as well. This group is likely to include subjects considered to be non-responders to chrysotherapy.

Table IV *Comparison of renal function studies between conventional (C) and adjusted (A) chrysotherapy groups*

Cumulative dose (g.)*	*0–1*		*1–2*		*2–3*	*3–8*
Type of therapy	*C*	*A*	*C*	*A*	*Adjusted‡*	*Adjusted‡*
Creatinine clearance (ml./min./m.^{2})	98	100	97	96	100	91
No. of patients	10	11	6	9	9	16
No. of determinations	25	29	7	11	9	31
Pitressin concentration (Osm/l.)	0·748	0·711	0·674	0·717	0·737	0·762
No. of patients	10	9	8	3	5	17
No. of determinations	12	11	8	3	6	26

* Total dosage of administered sodium aurothiomalate.
‡ Patients on conventional therapy were routinely crossed over to adjusted therapy at 60 weeks (average cumulative dosage of 1,564 mg.).
Urinary protein excretion >400 mg/TV was not observed (see text).

Table V *Results of adjusted and conventional gold therapy each in nine patients from 20 to 60 weeks*

Criterion		*Measurements*		*Statistical analysis*
		Adjusted group	*Conventional group*	
Range of joint motion	No. of joints	252	252	*P < 0·05
	No. improved at 60 wks	165	110	*H = 4·304
	No. worse	87	142	
Grip strength	No. of tests	18	18	
	No. improved	10	5	**P < 0·01
	No. worse	8	13	
Erythrocyte sedimentation rate (mm./1st hr) (Wintrobe)	No. of tests	36	36	*P < 0·01
	Mean at 20 wks	33·2	36·0	*H = 8·24
	at 60 wks	27·0	34·2	
Rheumatoid factor titre	No. seropositive at 20 wks	8	8	*P < 0·05
	Decline in titre at 60 wks	7	5	*H = 2·93
	Total decline (tube dilution)	27	12	
Steinbrocker functional index†	No. improved at 60 wks	3	1	**P 0·10
	No. worse	2	6	
	No. unchanged	4	2	
	Net change	+3	−5	

* Kruskal Wallis one-way analysis of variance.
** Fisher's 'F' test.
† Steinbrocker, Traeger, and Batterman (1949).

(3) Such patients may, however, respond to therapy if gold administration is continued and the dosage adjusted to achieve the specified serum gold concentration.

(4) The beneficial response to chrysotherapy is more likely to be sustained if the serum gold concentration is maintained at or above 300 μg. per cent.

Summary

Serum gold levels, clinical response, and toxicity studies were compared in eighteen patients assigned on a random basis to receive chrysotherapy on either a fixed (conventional dosage) or individual (adjusted dosage) therapy schedule. Dosage for the latter group was adjusted on the basis of serum gold levels to maintain values above 300 μg. per cent. Levels were monitored at weekly intervals by atomic absorption analyses. Significant differences in mean serum gold levels were recorded between the two therapy regimens: 136 *v.* 322 μg. per cent.

Adjusted dosage therapy in some patients was continued for more than 4 years. The higher serum gold levels recorded for this group reflect the more sustained and larger dosages, but the incidence and severity of adverse reactions was not increased. Significant clinical benefits were recorded in subjects receiving adjusted dosage when compared with the group on the fixed dosage schedule.

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