Clinical response and serum gold levels in chrysotherapy

Lack of correlation

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Since the inception of gold therapy for rheumatoid arthritis, methods have been sought to improve drug efficacy while minimizing undesirable side-effects. Efforts to accomplish this have included the measurement of urinary gold excretion (Jones, Ahmed, and Chan, 1971) and attempts to individualize gold dosage based on the clinical responses of the patients wherein dosage is increased until either beneficial effect or toxicity occurs (Smith, Pea, Kron, Hermann, Del Toro, and Goldman, 1958). More recently, another effort to improve the precision of gold therapy by the monitoring of serum gold levels (Rothermilch, Bergen and Phillips, 1967; Lorber, Chang, Friou, and Starr, 1969) has been proposed. In order to correlate clinical response with serum gold levels under routine clinical conditions, we have followed serial serum gold levels in 39 patients receiving conventional dosage chrysotherapy in our clinics; these patients were treated by our house staff in the same way that similar patients have been managed during the past 10 years.

Material and methods

Serial serum gold concentrations of consecutive patients undergoing gold therapy in our clinics were studied prospectively over a 12-month period. Generally, patients were selected to receive gold therapy if they had not responded sufficiently well to a conservative regimen of adequate salicylates, rest, physical therapy, and splinting. These patients all had classical or definite rheumatoid arthritis by ARA criteria (ARA, 1959). Serum gold determinations were made by atomic absorption spectrophotometry (Lorber, Cohen, Chang, and Anderson, 1968) on serum drawn just before gold injections at each visit. The standard deviation of determinations done in blind fashion on aliquots of a standard serum specimen containing 300 μg . gold per 100 ml. was $\pm 24.1 \mu\text{g}/100 \text{ ml}$.

Conventional fixed-dose chrysotherapy was employed as outlined by Freyberg (1966); after test doses, patients were given 50 mg. sodium aurothiomalate weekly by

intramuscular injection. The physicians treating the patients were unaware of the serum gold levels, and decisions regarding dosage changes or cessation of therapy were not influenced by serum levels. Under supervision of attending rheumatologists, individual patients were usually treated by more than one primary physician during a course of chrysotherapy. It is our policy to continue gold injections indefinitely in patients who are judged to benefit from gold. After attaining a total dose of 1 g. gold compound, most patients with a favourable response were then maintained with less frequent injections (Soler-Bechara, Kammerer, Rogoff, and Freyberg, 1965). Patients who did not improve after a total dose of 1 g. gold compound discontinued chrysotherapy, and were considered to be treatment failures.

After monitoring serum gold levels for 12 months, the charts were reviewed retrospectively, and some of the patients were examined by one of us (R. G.) in order to categorize the clinical response. Patients were judged to have no response if gold treatment had been discontinued, in the absence of toxicity, because of patient or physician dissatisfaction with the clinical response. This decision was usually based on conventional criteria of continued active inflammation or progressive increase of disability. Patients were categorized as having a satisfactory response to gold if they were still receiving gold treatment (and the total dose was greater than 1 g.), or if their disease clearly exacerbated 3 to 12 weeks after cessation of injections and improved again when chrysotherapy was recommenced. Patients were defined as having a toxic response if they developed a rash, leucopenia, or thrombocytopenia related to chrysotherapy which required discontinuance of gold. Significant nephrotoxicity was not seen in these patients but would have been an indication for stopping treatment if it had occurred.

"Steady state" is defined as that period during the treatment of an individual patient, using a standard dose schedule, when serum gold levels (at a given time after injection) achieve a stable plateau, and are predictable and nearly equal. Thus, a patient receiving 50 mg. gold compound weekly has achieved a steady state when his serum gold levels, measured 7 days after each injection, no longer increase from week to week, but instead remain relatively constant. Similarly, a patient on a fortnightly injection

schedule of a given dose will achieve a steady state after a period of time, so that serum gold levels taken 14 days after each injection are nearly equal on serial occasions.

Results

Data on clinical response and serum steady state values were obtained for 39 patients (22 men and 17 women). Clinical characteristics at the time therapy was begun and mean serum gold values of patients at steady state are grouped according to the type of clinical response (Table). Means value of serum obtained 7 days after injection ranged from 167 to 560 $\mu\text{g./100 ml.}$ at steady state. The time required to achieve a steady state after the start of gold treatment or a major change in dosage schedule was 5 to 10

weeks (Figure). In our patients there is no statistical correlation between serum gold levels and the efficacy or toxicity of gold therapy.

Discussion

In patients managed in a routine manner in our arthritis clinics, there is no correlation between serum gold levels at steady state and clinical response (as judged by conventional techniques) or any of the well-recognized toxic manifestations of gold.

Serum gold concentrations result from complex dynamics involving dosage schedule, rate of absorption from injection sites, excretion rates, plasma volume, and equilibration with tissue gold stores. The relationship of serum gold concentration to tissue gold content is not known. Mean serum gold levels do not correlate with total body retention of a radioactive gold tracer (Gerber, Paulus, Bluestone, Pearson, and Blahd, personal communication). Tissues vary greatly in their gold content (Jeffrey, Freundlich, and Bailey, 1968; Gottlieb, Smith, and Smith, 1971a). The relation of serum gold concentration to the concentration of gold at sites where its beneficial action is exerted is unknown, just as the sites of action are unknown.

The kinetics of serum gold during the days immediately after injection have been well described (Freyberg, Block, and Levey, 1941). More recently, it has been appreciated that serum levels at any given interval of time after each gold injection rise until a predictable level or steady state ensues (Rothermilch and others, 1967). At steady state, levels obtained at a given time after injection vary little on successive occasions. Therefore, it is reasonable to study serum levels during steady state for possible clinical correlation.

Tissue content of gold may not be constant even though serum levels are at steady state, as herein defined. In a number of patients studied, when serum

FIGURE Graph showing gold levels in a single patient measured 7 days after each injection. Note 'steady state' beginning at 9th week after beginning of gold therapy

Table Characteristics and mean serum gold concentrations of patients grouped according to clinical responses

Response	Satisfactory	None	Toxic
Mean age (yrs) ($\pm$ S.D.)	44.5 $\pm$ 13.3	49.2 $\pm$ 16.3	51.3 $\pm$ 12.6
Sex	16 M; 8 F	3 M; 5 F	3 M; 4F*
Mean duration of RA (yrs) ($\pm$ S.D.)	6.7 $\pm$ 6.3	9.2 $\pm$ 4.2	11.6 $\pm$ 12.8
Mean RF titre (latex agglutination)	1:2560	1:2560	1:10240
Mean ESR ($\pm$ S.D.)	40.8 $\pm$ 10.3	47.0 $\pm$ 9.2	40.0 $\pm$ 3.2
Mean serum gold at steady state ($\mu\text{g./100 ml.}$) ($\pm$ S.E.M.)			
7 days†	331.5 $\pm$ 23.7	408.3 $\pm$ 69.3	350.0 $\pm$ 49.5
14 days‡	167.7 $\pm$ 25.6	267.0 $\pm$ 42.6	172.5 $\pm$ 30.0

* Four patients with dermatitis, two with leucopenia, and one with thrombocytopenia.

† Serum taken 7 days after injection in patients on weekly injection schedule.

‡ Determined 14 days after injection in patients on fortnightly regimen.

steady state usually exists, Gottlieb, Smith, and Smith (1971b) found a mean gold excretion amounting to only 39 per cent. of the injected dose. Hence, in a patient receiving 50 mg. gold salt weekly, about 20 mg. were excreted in the urine and stool. Presumably the remaining 30 mg. was sequestered in tissue compartments, and the gold content of these tissues was increasing in the face of steady state serum levels. In this respect, gold kinetics may be similar to those of iron in haemochromatosis (Finch, 1949).

Individuals may vary in their responsiveness to a given concentration of gold. Krusius, Markkanen, and Peltola (1970) reported a statistical correlation between serum gold level and clinical response. However, their study differs from ours in that gold determinations were made by neutron activation analysis and that determinations for an individual patient were made during a single week early in the gold therapy regimen, before the establishment of a

steady state. Like us, they found a considerable overlap in the serum gold levels of patients grouped according to clinical responses.

Summary

In a study of unselected consecutive patients undergoing fixed-dose gold therapy for rheumatoid arthritis designed to reflect routine management in our clinics, the serum gold concentrations in 39 patients, measured by atomic absorption spectrophotometry at steady state (when repeated serial values at a given time after injection were nearly equal and thus predictable), showed no significant relationship to clinical response or toxicity. Serial determinations over a period of weeks did not correlate with beneficial effect or toxicity from gold therapy in our patients. These conclusions differ from currently published reports.

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