

Serum gold

II. Levels in rheumatoid arthritis

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Using the method described in the preceding paper (Dietz and Rubinstein, 1973), we have measured serum gold in 63 patients with rheumatoid arthritis in all phases of treatment with gold salts. This paper reports the results.

Methods

SERA

All but five of the 63 subjects were males. Most were drawn from the Rheumatology Service at the Veterans Administration Hospital; a few came from the Rheumatology Service at Loyola University Hospital. Patients were started on either Myochryesine (gold sodium thiomalate in water) or Solganal (gold thioglucose in oil) with weekly intramuscular injections of 25 or 50 mg. The gold content of both salts is 50 per cent. (w/w). In cases in which the patient was doing well, the frequency of injection was decreased at about 3-monthly intervals to 2, 3, and eventually every 4 weeks. In the presence of active synovitis, the injections were continued every 2 weeks. In some cases, after one gold salt had been given and stable blood levels achieved (see below), the other gold salt was substituted. The drug was stopped because of long-term remission, apparent lack of effect after a trial of at least 4 months, or toxicity.

10 ml. blood were drawn at various times after injection and the separated serum was frozen until analysed.

GOLD ANALYSIS

The method described in the previous paper was used. For approximately the first half of the study the Jarrell-Ash atomic absorption spectrophotometer was used and for the latter half the Perkin-Elmer instrument; from time to time the two instruments were checked against each other.

Results

Gold levels after first injection

Fig. 1 shows the serum levels of gold at 1, 3, 8, and 24 hrs after the initial intramuscular injection of 25 and 50 mg. of Myochryesine. The levels rise quickly, reach their maximum 3 hrs after the injection, and

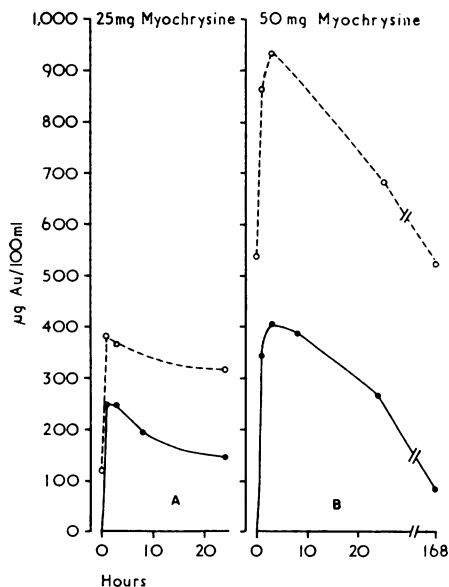


FIG. 1 Acute changes in serum gold after Myochryesine. The solid curves denote patients after the first intramuscular injection of Myochryesine, and the dashed curves patients on maintenance therapy. Each curve represents a different patient.

Of the two patients on maintenance therapy, the one who received the 25-mg. dose had previously received 1,025 mg. Myochryesine over a period of 1 year, the last dose of 25 mg. 3 weeks earlier.

The upper curve on the right represents a patient who had previously received 445 mg. Myochryesine over a period of 11 weeks, with the last dose of 50 mg. 1 week earlier. This last patient had consistently high gold levels one week after injection, 470–540 µg./100 ml. serum

slowly decline. The Figure also shows a similar result in two patients on maintenance gold therapy. In both circumstances at the end of 1 week the serum gold level approaches the level before the injection.

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Fig. 2 gives similar curves after the intramuscular injection of 25 and 50 mg. Solganal. As expected, the oil base permits slower absorption; the peak concentrations are lower, but the maximum levels are maintained for at least 24 hrs before they decline so that at 7 days they are about the same as those found 1 week after the Myochryesine injections.

Gold levels after repeated injection

After repeated weekly injections, the serum concentration just before the next injection gradually rises

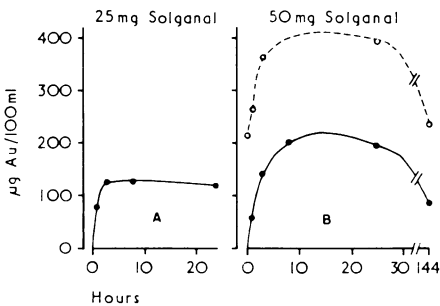


FIG. 2 Acute changes in serum gold after Solganal. See legend to Fig. 1.

The patient on maintenance therapy had previously received 425 mg. Myochryesine followed by 310 mg. Solganal, the last injection of 50 mg. Solganal 7 days earlier

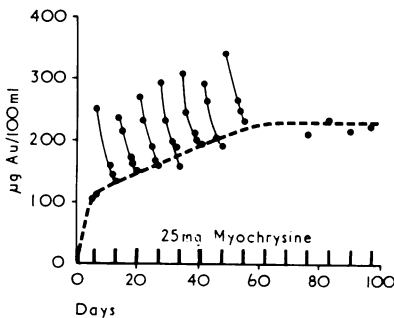


FIG. 3 Serum gold levels in a patient receiving 25 mg. Myochryesine weekly. The dashed curve joins the levels 7 days after the last injection. The solid curves represent gold levels at shorter intervals between the injections, the earliest being 24 hrs after the injection

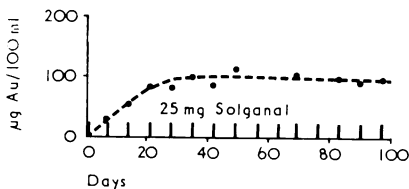


FIG. 5 Serum gold levels in a patient receiving 25 mg. Solganal weekly. The blood was drawn just before the weekly injection

and eventually reaches relative stability. The level of stability varies with the patient and the dose, and occurs earlier with Myochryesine than with Solganal. Individual examples of this are shown in Figs 3 to 6 for 25 and 50 mg. of Myochryesine and Solganal.

The individual variation in the concentration reached after regular weekly injection is shown in Table I (overleaf), which gives mean values and standard deviations of weekly gold determinations in five subjects receiving weekly injections of 25 mg. Myochryesine. The mean value ranged from 110 to 323 µg. Au/100 ml. with standard deviations about twice that found in precision studies of a single sample. A large part of the variability in serum level between patients is clearly due to weight differences, as indicated by the correlation coefficient between weight and serum level.

Figs 7 to 10 (overleaf) give a composite picture of the results obtained after stability of serum level was achieved after regular periodic administration of 25

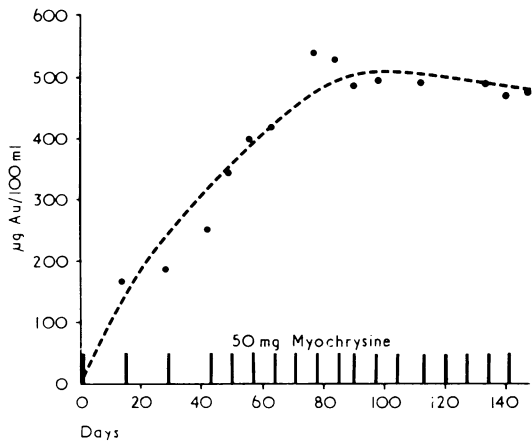


FIG. 4 Serum gold levels in a patient receiving 50 mg. Myochryesine weekly. The blood was drawn just before the weekly injection

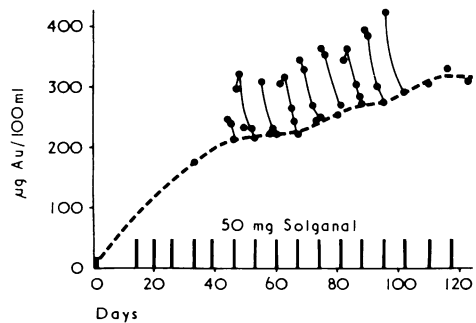


FIG. 6 Serum gold levels in a patient receiving 50 mg. Solganal weekly. See legend to Fig. 3

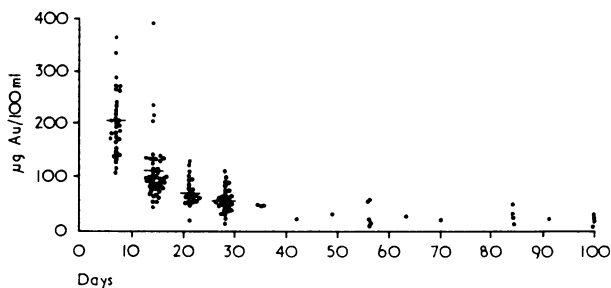
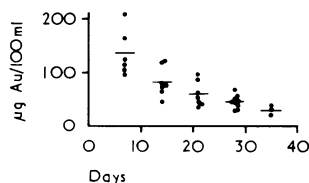
Table I Average serum gold levels in five patients on long-term therapy; values obtained 7 days after administration

Patient	Wt (kg.)	Myochrysin (mg./wk)	Total dose at start (mg.)	N	Mean		
					$\mu\text{g. Au}/100\text{ ml.}$	S.D.	C.V. (%)
A	81	25	350	14	110	15	13.6
B	69	25	250	13	121	18	14.9
C	65	25	375	10	323	32	9.9
D	79	25	200	13	134	20	14.9
E	62	25	200	14	279	34	12.2

N = number of successive weekly specimens.

S.D. = standard deviation.

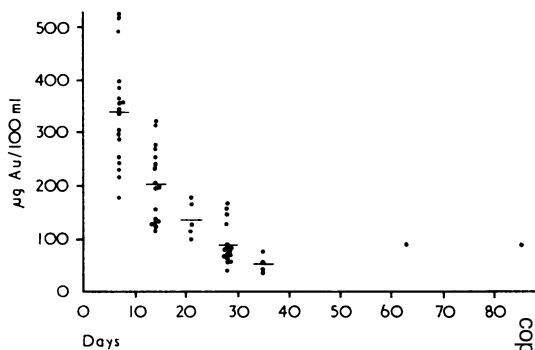
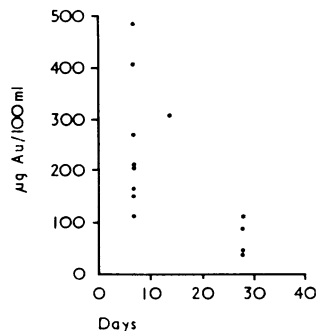
C.V. = coefficient of variation.

When weight was plotted against mean serum level, $r = 0.80$, significant at the 5 per cent. level.**FIG. 7** Serum gold levels at various intervals after the last injection of 25 mg. Myochrysin. All patients had reached a stable serum level at injection intervals of 7, 14, 21, or 28 days. Each point represents one individual although it may be the average of several determinations. The horizontal bars give the mean values**FIG. 9** Serum gold levels at various intervals after the last injection of 25 mg. Solganal. See legend to Fig. 7

and 50 mg. of Myochrysin and Solganal. At both dose levels the decrease in gold concentration with time is initially rather rapid but small amounts of gold persist for several months or longer after stopping administration.

Comments

The results given here are similar to those others obtained by neutron activation analysis (Krusius, Markkanen, and Peltola, 1970) and by atomic absorption (Lorber, Cohen, Chang, and Anderson, 1968; Mascarenhas, Granda, and Freyberg, 1971; Silverberg, Kidd, Shnitka, and Ulan, 1970). In

**FIG. 8** Serum gold levels at various intervals after the last injection of 50 mg. Myochrysin. See legend to Fig. 7**FIG. 10** Serum gold levels at various intervals after the last injection of 50 mg. Solganal. See legend to Fig. 7

particular, Fig. 8 is quite similar to the data shown in Fig. 3 in the paper of Lorber and others (1968).

During the period of study, four of our patients developed signs of gold toxicity requiring discontinuation of treatment; two had skin eruptions only, one had nephrotic syndrome only, and one had both. All were on weekly injections. The data on these patients are given in Table II (opposite). The serum gold levels at the time of toxicity varied from 95 to 365 $\mu\text{g.}/100\text{ ml.}$; these levels are in the range experienced by other subjects without toxicity (Figs 7 to 9). This agrees with the experience of others (Lawrence, 1961; Rothermich, Bergen, and Philips, 1967; Silverberg and others, 1970), although several authors have

Table II Data on four patients with gold toxicity

Patient	Salt	Frequency	Weekly dose (mg.)	Total dose (mg.)	Toxicity	Serum gold level ($\mu\text{g./100 ml.}$)	Eosinophils (%)
1*	S	Weekly	25	475	Skin	170	1
2	M	Weekly	50	550	Skin	365	7
3	M	Weekly	25	725	Renal	210	3
4	S	Weekly	25	375	Skin; Renal	95	2

S = Solganal, M = Myochrysin.

* One year later this patient was given several weekly injections of Myochrysin and developed rash and proteinuria.

indicated that high levels do correlate with toxicity (Krusius and others, 1970; Freyberg, 1966).

It has been suggested (Krusius and others, 1970; Lorber, Bovy, and Chang, 1971) that improvement after gold injection is more likely to be seen with relatively high serum levels. Although no formal attempt was made to study this question, at the conclusion of the study we classified 25 subjects who had been receiving very long-term injections of 25 mg. of Myochrysin weekly into good, fair, and poor response categories, based on the overall clinical assessment without reference to the serum gold values. Fifteen had a good response, and ten fair or

poor responses. The distribution of mean serum gold levels in both groups is shown in Fig. 11. Including the one strikingly high value in Group A, the mean of all values in this group was 215 $\mu\text{g./100 ml.}$; the corresponding figure in Group B was 164. This difference was not significant. If the very high value in Group A was left out, the mean for this group was 189. We are thus unable to confirm a clear relation between height of serum gold level and likelihood of clinical improvement, but the question would be better answered by an appropriate prospective study.

Summary

After the initial injection of a gold salt the serum level rises sharply and decays over the next week. The peak is higher and the dropoff faster with an aqueous salt (gold sodium thiomalate) than with an oily preparation (gold thioglucose in sesame oil). With weekly injection there is a continuous rise in the basal value for several months, after which the serum level is relatively stable. There is considerable individual variation in the level found after a standard weekly dose of gold salt. When the period between injections is lengthened, there is a steady decline in gold levels, although small amounts may be found in the serum for months. Patients with toxic reactions to gold have serum values in the normal range. A retrospective analysis failed to show a clear relation between height of serum gold level and clinical response, but it will take suitable prospective studies to clarify this important point.

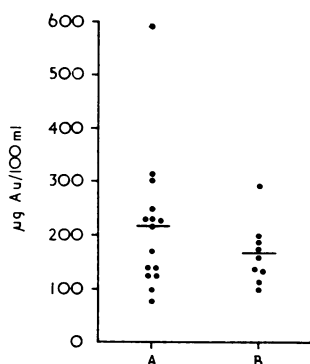


FIG. 11 Distribution of average serum gold levels in 25 patients on long-term injection of 25 mg. Myochrysin weekly.

A. 15 patients retrospectively judged as having done well

B. 10 patients retrospectively judged to have done poorly

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