Plasma levels and urinary excretion of gold during routine treatment of rheumatoid arthritis

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In the treatment of rheumatoid arthritis (RA) by gold, it has been customary to administer the gold by weekly injections of equal amounts, *e.g.* 50 mg. sodium aurothiomalate weekly (Freyberg, 1957). According to reports in the literature the percentage of satisfactory therapeutic results may vary from 23 to 85 per cent., and the percentage of toxic reactions from 5 to 62 per cent. (Fraser, 1945; Freyberg, 1966).

Gold levels in blood and urine may change from one day to another after gold injections, but the differences between individual patients receiving the same treatment and their relationships to the therapeutic effect have received little attention. Freyberg, Block, and Levey (1941) assayed the gold content of plasma and urine after injections of different gold preparations and during toxic reactions, but found no correlation with the plasma gold level. The same conclusion was drawn by Lawrence (1961) in studies with radioactive gold. Smith, Peak, Kron, Hermann, Del Toro, and Goldman (1958), however, found that a poor therapeutic effect was related to a high urinary excretion of gold and toxic reactions to a low excretion; they performed no gold assays of the blood.

In the present study, gold levels in blood and urine were determined in 25 patients with rheumatoid arthritis who were receiving gold therapy, and correlated with therapeutic effect and toxic reaction.

Material and Methods

All the 25 patients studied were suffering from classical rheumatoid arthritis according to the ARA diagnostic criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959). All were in an active stage of the disease, with functional grades II and III (Steinbrocker, Traeger, and Batterman, 1949). The erythrocyte sedimentation rate varied from 13 to 103 mm./1st hr, and the number of affected joints from two to twelve. Both the Waaler-Rose and the latex-fixation test were positive in nineteen cases, and

the latter only in three; both were negative in three cases.

The therapeutic effect, good (Grades I to III) or poor (Grade IV), was evaluated after 6 months' therapy from changes in the stage of RA according to the ARA criteria. Complications due to gold therapy were also registered.

Sodium aurothiomalate (Myocrisin) was given intramuscularly in doses beginning with 10 mg., 20 mg., 20 mg., and then 50 mg. once a week for 12 to 16 weeks and thereafter at longer intervals, usually once a month, according to the therapeutic effect. The dosage of anti-inflammatory drugs was kept constant throughout the study: none of the patients received corticosteroids.

The plasma gold content and the urinary gold excretion were assayed during the week after the second injection of 50 mg. Myocrisin (equal to 25 mg. gold). At that time the patients had received a total of 150 mg. Myocrisin (75 mg. gold). The gold content was studied on the 1st, 3rd, 5th, and 7th days after the injection, and also in a control specimen taken on the morning before the injection.

In four patients on long-term treatment with one injection a month, the gold assay was made three to six times during one month.

In five patients with toxic symptoms the gold estimates were made repeatedly in the course of 3 weeks.

Gold estimations were performed in duplicate by neutron activation analysis in an atomic research pile (Triga reactor, Otaniemi, Finland), by partial chemical separation of the activated gold, and by spectrometric quantitation of the gamma energy peak of the radiogold in a multichannel analyser.

Results

During the first day after the injection the average plasma gold content (Fig. 1, opposite) increased from 1.8 (range 1.2 to 4.0) $\mu\text{g./ml.}$ to 5.7 (range 3.2 to 8.0) $\mu\text{g./ml.}$; it then declined during the following days to a level somewhat higher than before the injection (mean 3.1 $\mu\text{g./ml.}$). The levels on the same days varied in individual patients by two to five-fold.

FIG. 1 Plasma gold levels during the week (1st, 3rd, 5th, and 7th day) after the second injection of 50 mg. sodium aurothiomalate.

During the first day after the injection the plasma gold content was similar in all groups. From the third day, the patients with the lower statistically significant level ($P < 0.01$) were those with the poor therapeutic response (Table). Those who subsequently developed toxic reactions had significantly higher levels on the 7th day ($P < 0.05$).

The urinary excretion of gold (Fig. 2) during the week after injection also showed considerable variations. To some extent, however, it appeared to depend on the plasma level, being higher in patients with a high level and lower in those with a low level. Those who subsequently developed toxic symptoms showed initially high urinary excretion rates.

The findings in the four patients on long-term treatment (Fig. 3, overleaf) who were receiving an injection once a month were somewhat similar. The patient with a poor therapeutic response (0-0) had the lowest plasma and urinary excretion values. Plasma levels remained persistently high during the 3 weeks

FIG. 2 Correlation between plasma gold content on 7th day after injection of 50 mg. sodium aurothiomalate and urinary excretion of gold on 4 of the 7 days after injection.

of study in the patients who showed toxic reactions. Clinical evaluation of disease activity at the begin-

Table Plasma gold level after the second injection of 50 mg. sodium aurothiomalate (Mean $\pm$ SE). Difference from "Good" group statistically significant only when indicated ($P < 0.05$)

Therapeutic effect	Day				
	0	1	3	5	7
Poor or none	1.35 $\pm$ 0.13	4.65 $\pm$ 0.40 $P \leq 0.05$	2.95 $\pm$ 0.26 $P \leq 0.01$	2.78 $\pm$ 0.36 $P \leq 0.01$	1.75 $\pm$ 0.43 $P \leq 0.01$
Good	1.86 $\pm$ 0.21	6.15 $\pm$ 0.39	4.34 $\pm$ 0.23	3.75 $\pm$ 0.16	3.13 $\pm$ 0.21
Complications	2.16 $\pm$ 0.45	5.64 $\pm$ 0.53	4.75 $\pm$ 0.51	4.14 $\pm$ 0.32	3.72 $\pm$ 0.18 $P \leq 0.05$

FIG. 3 Plasma gold levels and urinary excretion of gold in four patients treated with 50 mg. sodium aurothiomalate intramuscularly at monthly intervals.

ning of the study, the erythrocyte sedimentation rate, the number of joints involved, and the results of serological tests were not significantly different in patients having good or poor therapeutic responses or toxic reactions. All those with toxic reactions showed a good therapeutic response.

Discussion

The gold levels in the plasma seem to be rather high in this study. This may be due to a more accurate method of estimation, the standard deviation between duplicate determinations being $\pm 0.1 \mu\text{g.}$ which agrees with that given by Sølvsten (1964) and Lorber, Cohen, Chang, and Anderson (1968). There may be some correlation between the subsequent good or poor therapeutic response and the high or low plasma gold level from the third day after injection. On the other hand, the toxic reactions also show some correlation with the higher plasma gold levels. The plasma gold levels at the beginning of the treatment may therefore have some prognostic value.

A higher rate of excretion of gold into the urine, about one fourth of the injected dose, seems to be related to a high plasma gold level, and not with a low level as supposed by Smith and others (1958). On the contrary, a lower rate, less than one eighth of the dose injected, seems to be linked to a low

plasma level, but the correlation is poor. There is thus no clear justification for increasing the dosage in patients with a high urinary gold excretion, as proposed by Smith and others. Because of the overlap between the different groups, however, it is not always possible to assess the plasma gold levels from the urinary gold excretion.

The results reported by Lawrence (1961) indicate a higher gold concentration in inflamed than in normal joints, but we found no clear correlation between the plasma gold levels and the number of inflamed joints or the immunological status as indicated by serological tests. Further studies of the binding and metabolism of different gold preparations are required.

The question why higher gold levels are correlated with better therapeutic effects also needs further study. The plasma gold concentrations are effective in inhibiting the growth of some pathogenic bacteria, such as the Group A haemolytic streptococci (Rothbard, Angevine, and Cecil, 1941) and the PPLO-organisms causing arthritis in test animals (Sabin and Warren, 1940). They also inhibit the activity of some lysosomal enzymes (Persellin, Smiley, and Ziff, 1963) and may function as immunosuppressive agents. Further studies are needed to discover whether an increase in gold dosage in patients with low plasma levels would give better therapeutic results.

Summary

Plasma gold levels and the urinary excretion of gold were studied in 25 patients with active rheumatoid arthritis. The gold estimation was performed by neutron activation analysis after the second injection of a therapeutic dose of 50 mg. Myocrisin, *i.e.* after a total dose of 150 mg. during 4 weeks.

Another series of four patients was studied during long-term treatment, in which the injections were given once a month.

There appeared to be notable differences in the plasma gold concentrations in individual patients. On the seventh day after injection high plasma levels were found in patients who subsequently showed good therapeutic responses. Those with toxic reactions had the highest values, and those with a poor response the lowest. In general, a low urinary excretion of gold was found in patients with low plasma levels and a poor therapeutic response.

The results suggest that more accurate gold dosage could be achieved by estimating plasma gold levels during treatment. Routine dosage gives variable levels, and the rate of urinary gold excretion is not sufficiently closely correlated to plasma gold levels to serve as a reliable measure of these variations.

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References

- FRASER, T. N. (1945) *Ann. rheum. Dis.*, **4**, 71 (Gold treatment in rheumatoid arthritis).
- FREYBERG, R. H. (1957) *J. chron. Dis.*, **5**, 723 (The place of gold compounds in the treatment of rheumatoid arthritis).
- (1966) 'Gold therapy for rheumatoid arthritis', in 'Arthritis and Allied Conditions', ed. J. L. Hollander, 7th ed., p. 302. Lea and Febiger, Philadelphia.
- , BLOCK, W. D., AND LEVEY, S. (1941) *J. clin. Invest.*, **20**, 401 (Metabolism, toxicity and manner of action of gold compounds used in treatment of arthritis: Human plasma and synovial fluid concentrations and urinary excretion of gold during and following treatment with gold sodium thiomalate, gold sodium thiosulphate and colloidal gold sulphide).
- LAWRENCE, J. S. (1961) *Ann. rheum. Dis.*, **20**, 341 (Studies with radioactive gold).
- LORBER, A., COHEN, R. L., CHANG, CHIA CHIN, AND ANDERSON, H. E. (1968) *Arthr. and Rheum.*, **11**, 170 (Gold determination in biological fluids by atomic absorption spectrophotometry: application to chrysotherapy in rheumatoid arthritis patients).
- PERSELLIN, R. H., SMILEY, J. D., AND ZIFF, M. (1963) *Ibid.*, **6**, 787 (Mechanism of action of gold salts).
- ROPES, M. W., BENNETT, G. A., COBB, S., JACOX, R., AND JESSAR, R. A. (1959). *Ann. rheum. Dis.*, **18**, 49 (American Rheumatism Association diagnostic criteria for rheumatoid arthritis. 1958 revision).
- ROTHBARD, S., ANGEVINE, D. M., AND CECIL, R. L. (1941) *J. Pharmacol. exp. Ther.*, **72**, 164 (The influence of gold sodium thiomalate (myocrisin) on the prevention of hemolytic streptococcus arthritis in rats).
- SABIN, A. B., AND WARREN, J. (1940) *J. Bact.*, **40**, 823 (The curative effect of certain gold compounds on experimental, proliferative, chronic arthritis in mice).
- SMITH, R. T., PEA, W. P., KRON, K. M., HERMANN, I. F., DEL TORO, R. A., AND GOLDMAN, M. (1958) *J. Amer. med. Ass.*, **167**, 1197 (Increasing the effectiveness of gold therapy in rheumatoid arthritis).
- SØLVSTEN, S. (1964) *Scand. J. clin. Lab. Invest.*, **16**, 39 (Determination of gold in serum and urine by neutron activation analysis).
- STEINBROCKER, O., TRAEGER, C. H., AND BATTERMAN, R. C. (1949) *J. Amer. med. Ass.*, **140**, 659 (Therapeutic criteria in rheumatoid arthritis).

RÉSUMÉ

Les taux plasmatiques et l'excrétion urinaire de l'or pendant le traitement de la polyarthrite rhumatoïde

Les taux plasmatiques de l'or et l'excrétion urinaire de l'or ont été étudiés chez 25 malades atteints d'arthrite rhumatoïde active. L'estimation de l'or a été faite par l'analyse de l'activation du neutron après la seconde injection d'une dose thérapeutique de 50 mg. de Myocrisine, c'est-à-dire après un total de 150 mg. durant quatre semaines.

Une autre série de quatre malades a été étudiée pendant un traitement à long terme, ils avaient reçu une injection par mois.

Il a semblé que des différences marquées étaient présentes dans les concentrations de l'or de chacun des malades pendant le septième jour après l'injection. Des taux plasmatiques élevés ont été rencontrés chez les malades qui ont eu plus tard de bons résultats thérapeutiques. Ceux montrant des réactions toxiques avaient les taux les plus élevés, et ceux qui manifestaient un résultat médiocre des taux les plus bas. En général une excrétion urinaire basse d'or a été vue chez les malades avec des taux plasmatiques bas et un résultat thérapeutique médiocre.

Les résultats suggèrent qu'un dosage plus exact d'or pourrait être réalisé en estimant les taux plasmatiques pendant le traitement. Le dosage habituel donne des taux variables et le taux urinaire n'est pas suffisamment en corrélation aux taux plasmatiques de l'or pour servir comme un facteur sûr de ces variations.

SUMARIO

Niveles de plasma y excreción urinaria de oro durante tratamiento rutinario de poliartritis reumatoide

Los niveles de oro en el plasma y la excreción urinaria de oro fueron estudiados en 25 pacientes con artritis reumatoide activa. El cálculo del nivel de oro se realizó por análisis de activación de neutrones después de la segunda inyección de una dosis terapéutica de 50 mg. de mio-crisina, es decir, al cabo de un total de 150 mg. durante cuatro semanas.

Otra serie de cuatro pacientes fue estudiada durante tratamiento a largo plazo, en el cual las inyecciones se administraron una vez al mes.

Parecía haber notables diferencias en las concentraciones de oro en el plasma en cada paciente al séptimo día después de la inyección. Se descubrieron altos niveles de plasma en pacientes que, más tarde, acusaron buenas reacciones terapéuticas. Aquellos que presentaban reacciones tóxicas tenían los valores más altos, y aquellos con una reacción pobre, los más bajos. En general se halló una excreción urinaria baja de oro en pacientes con niveles de plasma bajos y una reacción terapéutica pobre. Los resultados sugieren que podría lograrse una dosis más exacta de oro si se calculasen los niveles de oro del plasma durante el tratamiento. Las dosis de rutina arrojan niveles variables y la proporción de secreción urinaria de oro no está correlacionada con los niveles de oro del plasma como para servir de medida segura de estas variaciones.