Gold-binding Sites in the Plasma of Patients with Rheumatoid Arthritis Undergoing Treatment with Gold Sodium Thiomalate

W. E. SMITH, D. H. BROWN

Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, U.K.

and H. A. CAPPELL

Centre for Rheumatic Diseases, University Department of Medicine, Baird Street, Glasgow, U.K.

Received November 6, 1984

Gold compounds are among the most effective therapeutic agents for the treatment of rheumatoid arthritis but their use is limited both by toxicity and by the varied response of individual patients [1, 2, 4]. Possibly because gold does not appear to be essential to human life, there is no well-defined transport and storage system comparable to that for copper and, as a consequence, gold distributes widely in blood fractions and in tissues. An understanding of the chemistry producing these changes would be useful as an aid both to the understanding of the reasons for toxic and therapeutic effects and to the synthesis of more specific gold compounds. It is difficult to obtain *in vivo* information on gold chemistry but, from time to time, information from *in vivo* kinetics or distribution studies does provide some insight and we report one such observation here.

As part of a clinical trial, we measured the gold concentrations in separated plasma protein fractions from patients with rheumatoid arthritis who were undergoing therapy with gold sodium thiomalate (Myocrisin). The proteins were separated by electrophoresis and the gold concentrations measured by atomic absorption spectrometry using carbon furnace atomisation as described previously [4]. None of the patients had received gold therapy previously. The Myocrisin was administered by an injection of 50 mg at weekly intervals and samples for gold analysis were taken immediately prior to injection, so that the gold distribution would be as near equilibrium as possible. At the end of twelve weeks, the plasma gold level had reached a plateau level of about 2–3 mg of gold per ml of plasma, in agreement with previous studies.

To evaluate the effect of gold concentration on binding to various protein fractions, the distribution of gold between albumin and the globulins was calculated at different weeks when samples were available as the ratio:

TABLE I. Ratio of Gold in Grams per Gram of Albumin to Total Gold in Grams per Gram of Total Protein for Five Patients with Rheumatoid Arthritis given Weekly Injections of 50 mg Gold Sodium Thiomalate (Myocrisin).

Patient	Week	Ratio
1	2	0.96
	4	0.93
	8	0.91
	12	0.94
	16	0.96
2	2	1.32
	11	1.32
3	2	0.81
	4	0.79
	9	0.70
	2	0.98
	4	0.91
	12	1.10
5	3	1.40
	5	1.32

$$\frac{\text{gold in albumin in } \mu\text{g/ml}}{\text{gm of albumin present/ml}} \Big/ \frac{\text{gm in plasma } \mu\text{g/ml}}{\text{gm of plasma protein/ml}}$$

In spite of the fact that the gold concentration was continually rising with time, this ratio remained constant for individual patients but varied quite substantially between patients (Table I).

We have already shown that gold on the plasma proteins can be either tightly or loosely bound and that the loosely bound fraction, which is mainly on the albumin, is unchanged Myocrisin which is removed by electrophoresis [1]. Thus, the ratio is indicative of the behaviour of tightly bound gold, which is most likely to be present as gold(I) bound to sulphur ligands and which accounts for about 85% of the plasma gold.

The implication of these results is that the various gold receptor sites are in competitive equilibrium with the circulating gold compound and its metabolites. Since a plateau region is reached in the total plasma gold concentration, some form of equilibrium is achieved. Since there is no sign of any of the major plasma sites becoming saturated and altering the albumin to globulin gold ratio, it would seem that the gold level in plasma is maintained by an equilibrium between the absorption, storage and excretion processes.

The nature of the gold site on albumin has been investigated and the binding between the protein and the gold is quite strong. However, the highest ratio

0020-1693/85/$3.30

of gold to albumin achieved in this and other studies of total gold in serum are in the range from 1 to 10 to 1 to 20 gold atoms per albumin molecule. Thus, it would appear that the gold, present as a gold(I) complex is involved in a series of competing reactions involving substitution and exchange with such species as small molecule thiols, disulphides and metal thiolate complexes, protein and probably cell surfaces. These would be expected to potentiate the natural thiol equilibrium and through them enzyme and cellular activities. Studies of distribution and of enzyme function have been disappointing up to the present time in that neither the therapeutic or toxic action has been discovered. The results discussed here lead to the suggestion that non specifically bound gold atoms could well act by potentiating a range of thiol groups *in vivo*. This effect is likely to be greatest in specific areas such as the plasma cell membrane surface where the gold concentration held in the plasma is likely to be similar to the thiol concentration rather than areas such as cytosolic fluid where the thiol concentration is five hundred to one thousand times larger than the gold concentration.

References

1 D. H. Brown and W. E. Smith, *Chem. Soc. Rev.*, *9*, 217 (1980).
2 C. F. Shaw III, *Inorg. Persp. Med. Biol. 2*, 287 (1979).
3 P. J. Sadler, *Struct. Bonding (Berlin)*, *29*, 171 (1976).
4 J. C. Banford, D. H. Brown, R. A. Hazelton, C. J. McNeil, W. E. Smith and R. D. Sturrock, *Rheumatol. Int.*, *2*, 107 (1982).
5 C. F. Shaw, III, N. A. Schaeffer, R. C. Elder, M. K. Eidsness, J. M. Trooster and G. H. M. Calis, *J. Am. Chem. Soc.*, *106*, 3511 (1984).