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THE QUANTITATIVE DISTRIBUTION OF GOLD IN SKIN DURING CHRYSOTHERAPY

NEAL S. PENNEYS, M.D., PH.D., KARL KRAMER, M.D., AND NORMAN L. GOTTLIEB, M.D.

Department of Dermatology and the Arthritis Division, Department of Medicine, University of Miami School of Medicine, Miami, Florida

Gold concentrations in epidermis, dermis, and whole skin were measured by neutron activation analysis after formation of suction bullae in 8 patients who had received protracted chrysotherapy. Epidermis contained 3% (median) of the gold content of whole skin. A direct correlation between cumulative gold dose and skin gold level was noted. These findings suggest that apparent gold concentrations in skin are influenced by the depth of the biopsy, that keratinous tissues have little affinity for gold, and that the gold storage capability of skin is not saturated by large cumulative doses of gold. The beneficial effect of gold in pemphigus may not be mediated at the site of blister formation.

Pemphigus is an acantholytic blistering disease which may be managed successfully for extended periods of time with gold compounds [1]. An initial course of weekly gold injections, followed by a maintenance schedule of injections every 2 to 6 weeks, is associated with clinical improvement or remission, and reduction of antiepithelial antibody titer in the majority of patients [2]. The loci and mechanisms of gold action in pemphigus are unknown. The findings of gold deposition in skin [3], and the higher skin gold concentrations resulting from prolonged chrysotherapy [4], raise the possibility that the site of gold action is in the skin. The quantitative distribution of gold within whole skin has not been described previously.

We report the results of a study in which suction blisters were induced in 8 patients with rheumatoid arthritis (RA) who had received protracted chrysotherapy. Gold concentrations in epidermis, dermis, and whole skin were measured using neutron activation analysis.

MATERIALS AND METHODS

Suction blisters were raised on the upper thighs of 8 patients with definite or classic RA [5] who had received a mean dose of 6,964 mg of gold sodium thiomalate (Myochrysine)* or aurothioglucose (Solganal)* over a mean of 6.8 years. These patients were selected for study, in contrast to gold-treated pemphigus patients, because of the large cumulative doses of gold they had received (with one exception). Some characteristics of the patients and their course of treatment are shown in the Table. Blisters were raised at room temperature in a standard manner using a simple piston-type suction apparatus composed of a plastic cup attached to a syringe in series with a pressure gauge. Generally a bulla was produced after 30 to 60 min of suction. The blister roof (epidermis) was removed with sterile stainless-steel scissors, weighed in a Mettler balance, and placed in a preweighed acid-washed 0.9-ml polyethylene capsule. Four-millimeter punch biopsies of the base of the blister (dermis), and of the adjacent whole skin, were taken and similarly handled. Capsules with enclosed specimens were dried for 6 hr under an infrared heat lamp and tissue dry weight measured. Gold content in all specimens was determined by neutron activation analysis at the reactor facility of Union Carbide Corporation, Tuxedo, New York. Four empty capsules, and three capsules containing ashed fecal specimens of known gold content, were included for purposes of control. Each of the blanks had less than 5 ng of gold, while the fecal control specimens contained 4.59, 4.75, and 4.75 μg gold per gm ash, which was similar to results in previous studies in which 41 aliquots contained a mean of 4.6 ± 0.5 μg gold per gm ash.

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Reprint requests to: Dr. N. S. Penneys, Department of Dermatology, P.O. Box 520875, Miami, Florida 33152.

* Myochrysine is made by Merck, Sharp & Dohme; Solganal by Schering. Both compounds are approximately 50% gold by weight.

RESULTS

The concentrations of gold, given as micrograms of gold per gram of tissue wet weight, in epidermis, dermis, and whole skin are shown in the Table. Dermis contained higher levels of gold than whole skin in 6 of 8 patients. Epidermis contained 3% (median) of the whole-skin gold content. A higher percentage of the whole-skin gold was in the epidermis in patient A.H., as shown in the Table. This subject differed from the remainder of the group in at least two respects. She had the most intense course of chrysotherapy (50 mg of Solganal weekly for 17 consecutive weeks, increasing gradually to 100 mg weekly because of rapidly progressive, severe RA), and a much lower cumulative gold dose than all other patients (Tab.).

The relationship between cumulative gold dose and gold concentration in whole skin is shown in the Figure. Each point represents the result in a single patient. A direct correlation between skin gold concentration and total gold dose is observed.

TABLE. *Patient characteristics, course of gold treatment, and gold concentration in epidermis, dermis, and whole skin*

Patient	Age	Race	Sex	Duration RA (*yr*)	Duration chryso-therapy (*yr*)	Total dose gold compound (*mg*)	Mean yearly gold dose (*mg/yr*)	Gold concentration (μg Au/gm tissue wet weight)		
								Epidermis	Dermis	Whole skin
A.S.	59	W	F	10	7	12,720	1,817	3.2	42.1	43.7
E.W.	66	W	F	9	9	4,000	450	0.8	29.5	26.5
J.R.	53	W	F	27	5	7,270	1,454	0.7	29.4	26.3
S.K.	33	W	F	7	5	4,325	865	1.3	11.9	10.1
C.H.	60	W	M	22	9	5,840	633	—	12.9	10.5
K.D.	33	W	F	10	8	12,410	1,551	1.9	130.0	91.0
C.D.	67	W	M	15	11	7,420	675	0.8	56.0	83.0
A.H.	46	W	F	1.5	0.5	1,730	—	2.1	13.6	7.6

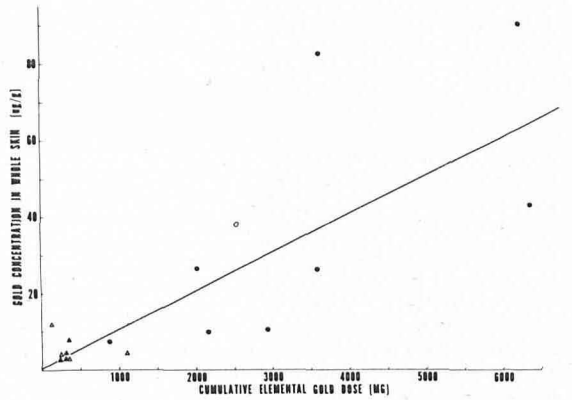

FIG. Gold concentrations in whole skin correlated with cumulative gold dose. Each point is the result from a single patient. The *solid circles* indicate patients in the present study. The *closed triangles* in the far left are the last biopsy data taken from the patients shown in Table 2 of our previous work [3]. The *open triangles* are the results of the control skin biopsies shown in Table 3 of this same report [3], while the *open circle* is the result of a control skin biopsy taken from another patient studied earlier (Table 2 in [4]).

DISCUSSION

This study shows that significant quantities of gold are deposited in skin during chrysotherapy, confirming earlier reports by ourselves [3,4,6], and others [7–10]. Although the distribution of gold in skin has been examined previously, using histochemical [10] and laser microprobe techniques [7], this is the first report in which gold concentrations in epidermis, dermis, and whole skin have been measured quantitatively using the most sensitive and precise method currently available, neutron activation analysis, and a blister technique that produces clean separation of epidermis from dermis.

Knowledge of the relative gold concentrations in epidermis and dermis is relevant to all studies seeking to correlate skin gold levels with other events such as the clinical response of RA [3] and pemphigus [6] to chrysotherapy, and gold dermatitis [3,9], because skin gold content may vary significantly according to the depth of the biopsy. The finding of low gold levels in epidermis supports our previous observation [3] that keratinous tissues have little affinity for gold, in contrast to other heavy metals such as lead and arsenic [11,12]. The dermal localization of gold may result from its localization in histiocytes [7], the slow turnover rate of dermal material [13], or the affinity of collagen for gold. Adam [14–16] found that gold binds to collagen, increases the number of collagen cross-links, and decreases collagen solubility, in rats.

Gold treatment beneficially influences the course of pemphigus [1,2]. Although the mechanisms of gold action remain unknown, the finding that gold localizes in dermis, and not epidermis, favors the hypothesis that its beneficial effects are not mediated locally. Although normal epidermal turnover is 14 days (basal cell layer to stratum granulosum) [17], many pemphigus patients can be managed successfully with infrequent gold injections, suggesting that significant gold accumulation above the basal cell layer is not necessary for a therapeutic response.

Of note in the Figure is the continuous rise in skin gold levels found with greater cumulative doses of gold, indicating the capacity of skin to store large quantities of gold, and the absence of a saturation effect. Additional factors, besides total gold dose, such as intensity and duration of gold treatment, and others yet to be defined, must influence skin gold levels as shown by the variability of skin gold concentrations at similar cumulative gold doses for individual patients. The mean gold level in the present study was 37.3 μg gold per gm of skin after a mean of nearly 3.5 gm of elemental gold, compared to 4.6 μg after 0.29 gm of gold in our earlier report. Using the mean of all data plotted in the Figure it may be calculated that approximately 0.011 microgram of gold is deposited in each gram of skin for every milligram of elemental gold injected intramuscularly. Assuming total body human skin weighs 3200 grams (females) [18], 35 micrograms of gold will deposit in skin for each milligram of gold administered.

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REFERENCES

1. Penneys NS, Eaglstein WH, Frost P: The long-term management of pemphigus with gold therapy. Arch Dermatol (in press)
2. Penneys NS, Eaglstein WH, Indgin S, Frost P: Gold sodium thiomalate treatment of pemphigus. Arch Dermatol 108:56–60, 1973
3. Gottlieb NL, Smith PM, Penneys NS, Smith EM: Gold concentrations in hair, nail and skin during chrysotherapy. Arthritis Rheum 17:56–62, 1974
4. Gottlieb NL, Smith PM, Smith EM: Tissue gold concentrations in a rheumatoid arthritic receiving chrysotherapy. Arthritis Rheum 15:16–22, 1972
5. Ropes MW, Bennett GA, Cogg S, Jacox R, Jessar RA: Diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 9:175–176, 1958
6. Penneys NS, Ziboh V, Gottlieb NL, Katz S: Inhibition of prostaglandin synthesis and human epidermal enzymes by aurothiomalate *in vitro*: possible actions of gold in pemphigus. J Invest Dermatol 63:356–361, 1974
7. Cox AJ: Gold in the dermis following gold therapy for rheumatoid arthritis. Arch Dermatol 108:655–657, 1973
8. Bogg A: Skin complications of gold treatment. Acta Rheum Scand 4:86–97, 1958
9. Freyberg RH, Block WD, Wells GS: Gold therapy for rheumatoid arthritis. Clinics 1:437–570, 1942
10. Cardis F, Conte M: La Chrysocyanose (Pigmentation cutanee apres injection de sels d'or). Ann Dermatol 7:229–244, 1936
11. Kopito L, Briley AM, Schwachman H: Chronic plumbism in children: diagnosis by hair analysis. JAMA 209:243–248, 1969
12. Althausen TL, Bunther L: Acute arsenic poisoning. JAMA 92:2002–2006, 1929
13. Neuberger A, Slack HGB: The metabolism of collagen from liver, bone, skin, and tendon in the normal rat. Biochem J 53:47–52, 1953
14. Adam M, Kuhn K: Investigations on the reaction of metals with collagen *in vivo*. 1. Comparison of the reaction of gold thiosulphate with collagen *in vivo* and *in vitro*. Eur J Biochem 3:407–410, 1968
15. Adam M, Fietzek P, Kuhn K: Investigations on the reaction of metals with collagen *in vivo*. 2. The formation of cross-links in the collagen of lathrytic rats after gold treatment *in vivo*. Eur J Biochem 3:411–414, 1968
16. Adam M, Bartl P, Deyl Z, Rosmus J: Uptake of gold by collagen in gold therapy. Ann Rheum Dis 24:378–381, 1965
17. Weinstein G, Van Scott EJ: Turnover time of human normal and psoriatic epidermis by autoradiographic analysis. J Invest Dermatol 45:257–262, 1965
18. Allen AC: The Skin. New York, Grune & Stratton, 1967, p 1