Oral chrysotherapy in rheumatoid arthritis: auranofin

Cleveland Clinic experience and literature review[1]

Daniel J. Mazanec, M.D.
Allen M. Segal, D.O.
Allen H. Mackenzie, M.D.
Mary Lippert, R.N.

Intramuscular gold therapy is a widely accepted form of treatment for active rheumatoid arthritis which fails to respond to salicylates or nonsteroidal anti-inflammatory agents. However, logistical concerns, uncommon but potentially serious renal and hematologic toxicity, and the relatively high long-term dropout rate mitigate against this form of therapy. Auranofin is an orally absorbed gold compound which differs significantly from intramuscular gold in terms of both pharmacokinetics and potential mechanisms of action. Clinical experience with auranofin is reviewed both at the Cleveland Clinic and worldwide. Therapeutic efficacy compares favorably with intramuscular gold and D-penicillamine, while significantly fewer patients are withdrawn from therapy due to toxicity (most commonly, diarrhea) than with intramuscular gold. Proteinuria and thrombocytopenia are considerably less common. Auranofin may prove to be valuable in the management of severe rheumatoid arthritis and offers several potential advantages over intramuscular gold therapy.

Index terms: Arthritis, rheumatoid • Gold, therapeutic use

Cleve Clin Q 52:123–128, Summer 1985

According to Rodnan and Benedek,[1] the use of gold compounds in the management of rheumatic disease probably has its roots in the work of Koch, who suggested in 1890 that gold cyanide compounds inhibit the growth of tubercle bacilli in vitro. In 1927, believing gold to be an antiseptic agent, Lande[2] extended the use of gold therapy to nontuberculous conditions such as subacute bacterial endocarditis and rheumatic fever. He was impressed by the relief of joint pain afforded by aurothioglucose and believed that gold was worthwhile in chronically febrile cases

[1] Department of Rheumatic Disease, The Cleveland Clinic Foundation. Submitted for publication Nov 1984; accepted Feb 1985. sjh

0009-8787/85/02/0123/06/$2.50/0

of painful arthritis resistant to usual treatment. Forestier[3] began using gold as gold-thiopropanol sodium sulfonate in rheumatoid arthritis in 1928 and by 1935 had treated more than 550 patients. A prospective trial of aurothioglucose was reported by Ellman and Lawrence in 1940,[4] using weekly dosage schedules of 200–300 and 100 mg. Patients given the higher dose responded best, but also experienced more adverse reactions. More than two thirds of the control patients responded upon being given a placebo.

In 1961, the Empire Rheumatism Council (ERC) of Great Britain published the final results of a multicenter trial in which modern intramuscular gold therapy was validated as having significant therapeutic benefit in patients with rheumatoid arthritis.[5] In 1974, Sigler et al[6] suggested that such treatment significantly retarded progression of rheumatoid arthritis as seen on radiographs.

Intramuscular gold therapy

Currently, therapeutic gold is available in two forms, both of which are administered intramuscularly: gold sodium thiomalate (Myochrysine, MSD), a water-soluble compound, and aurothioglucose (Solganal), an oil suspension. Both compounds are 50% gold by weight. Initially, they are administered on a weekly basis for approximately 20 weeks to a total dose of approximately 1 g; at that point, if no toxicity has occurred and treatment seems beneficial, the interval between injections is lengthened and therapy is continued indefinitely.

In the ERC trial, gold sodium thiomalate was administered over five months to a total dose of 1 g. Grip strength, joint count, and sedimentation rate improved significantly over 18 months of follow-up; however, 35% of patients had at least one toxic reaction, including dermatitis, stomatitis, mucositis, and corneal ulceration, and 14% were forced to discontinue therapy because of toxicity. A similar controlled trial by the Cooperating Clinics Committee of the American Rheumatism Association resulted in comparable findings: one third of the gold-treated patients were withdrawn from treatment due to toxicity.[7] Thus there is a relatively high dropout rate with intramuscular gold therapy due to toxicity within the initial five-month course. As many as 50% of patients who initially benefit from intramuscular gold therapy are withdrawn from treatment within five years due to toxicity or relapse.[8] In addition, the need for a weekly intramuscular injection preceded by four to five months of laboratory work has discouraged patient and physician alike. These and other concerns led to the search for an effective and possibly less toxic agent which could be absorbed orally.

Clinical pharmacology of auranofin

Auranofin is a monomeric compound with a central gold atom stabilized by two ligands: triethylphosphine and thiolate. It is 29% gold by weight and highly soluble in lipids. Pharmacokinetically, it is quite different from intramuscular gold, a fact that may well account for the lower frequency of serious toxicity. Tepperman et al[9] have recently studied the absorption of auranofin in vitro using an everted intestinal sac as a model. Their studies suggest that auranofin is deacetylated by the intestinal mucosa prior to absorption. Approximately 25% of oral auranofin is absorbed, compared to less than 1% for gold sodium thiomalate. Based on an average daily dose of 6 mg of auranofin, this would result in absorption of approximately 3 mg of gold per week, compared with 25 mg of injected gold (assuming 100% intramuscular absorption). This may account for the significantly lower serum gold levels (0.6 μg/ml) in auranofin-treated patients, compared with gold injections (7 μg/ml).[10] Walz et al[11] have noted that gold levels in rat kidneys are considerably lower after auranofin, compared with gold injections, which again may be related to the lower total dose of gold administered and may also be important in the lower incidence of nephrotoxicity seen with the oral preparation. Finally, 85% of a dose of auranofin is excreted per rectum, compared to 70% renal excretion of intramuscular gold.

The precise mechanism of action of all gold compounds, including auranofin, is unknown. However, it does possess significant anti-inflammatory, anti-arthritic, and immunoregulating properties. Injection of Freund's adjuvant into the hind paw of a rat results in the development of generalized, highly inflammatory polyarthritis within two to three weeks, particularly in the distal small joints of the paws and tail. This "adjuvant arthritis" provides a model for the study of anti-rheumatic compounds. Auranofin is as effective as gold sodium thiomalate in suppressing the inflammatory response as measured by hind leg volume.[12] A second inflammatory model

Table 1. Comparative immunomodulating effects of auranofin and gold sodium thiomalate

	Auranofin	Gold Sodium Thiomalate
Arthritis models		
Adjuvant arthritis	Decrease	Decrease
Carrageenan-induced edema of the paw	Decrease	No effect
Inflammatory cells		
Lysosomal enzyme release	Decrease	Decrease or no effect
Chemotaxis	Decrease	Decrease
Superoxide radical generation	Decrease	No effect
Cellular immunity		
Delayed hypersensitivity to oxalazone in mice	Increase	Increase
Delayed hypersensitivity to DNCB in humans	Decrease	No effect
Humoral immunity		
Polymorphonuclear antibody-dependent cellular cytotoxicity	Decrease	No effect
Polymorphonuclear antibody-dependent complement lysis	Decrease	Increase

involves injection of 1% carrageenan suspension into the hind paw of a rat, which is followed within one to three hours by local swelling and erythema. In this model, auranofin is effective in inhibiting inflammation as measured by paw volume, whereas gold sodium thiomalate has no effect.

Effects of auranofin on inflammatory cell function have been studied in vitro using various systems. DiMartino and Walz[13] demonstrated inhibition of lysosomal enzyme release by rat leukocytes by auranofin as assessed by β-glucuronidase and lysozyme markers. Wolach et al[14] evaluated inhibition of lysosomal enzyme release with auranofin in healthy volunteers and patients and confirmed DiMartino's in vitro findings. Similarly, both in vitro and in vivo studies have demonstrated inhibition of chemotaxis by both gold sodium thiomalate and auranofin, particularly with regard to mononuclear cells.[15] Generation of superoxide radicals, which are products of the inactivated phagocyte and important inflammatory mediators, is inhibited by auranofin, but not by gold sodium thiomalate.[16] Both in vitro and in vivo studies suggest that auranofin may either suppress or enhance the cellular immune response. In mice treated with auranofin, Walz and Griswold[17] demonstrated enhancement of the delayed hypersensitivity response to oxazolone, and similar enhancement was seen in animals treated with gold sodium thiomalate. Lorber et al[18] demonstrated suppression of skin test sensitivity to dinitrochlorobenzine (DNCB) in patients treated with auranofin whereas those receiving gold sodium thiomalate tested normally. Auranofin also affects humoral immunity, as evidenced by suppression of polymorphonuclear-mediated antibody-dependent cellular cytotoxicity[19] which is not inhibited by other gold compounds. Antibody-dependent lysis of complement is also inhibited by auranofin, whereas it is enhanced by gold sodium thiomalate. However, in vitro studies of the effects of auranofin must be interpreted with caution in view of the work of Tepperman et al,[9] suggesting that the drug is absorbed as the deacetylated metabolite. In vitro studies to date have employed the acetylated form of the drug. It is conceivable that effects on these various in vitro systems might be different with the deacetylated metabolite.

Clearly, the biological effects of auranofin are in some respects quite different or even opposite from those of intramuscular gold (*Table 1*). This would suggest that auranofin is not simply an oral version of intramuscular gold, but an entirely different compound which perhaps exhibits a different mechanism of action. This may have clinical significance in therapeutic decisions involving patients who have shown no improvement with intramuscular gold.

Cleveland Clinic experience

Eleven adults with active classical or definite adult-onset rheumatoid arthritis meeting the di-

Table 2. Cleveland Clinic experience: patients continuing auranofin

Patient No.	Age (yr) and Sex	Duration of Disease (yrs)	Durtion of Auranofin Therapy (mos)	Gel (hrs) Pre/Post	Functional Class Pre/Post	WESR* Pre/Post	Toxicity
1	52F	5	27	4/0	II/I	55/42	None
2	41F	5	27	1½/0	II/I	38/19	None
3	36F	1½	30	12/0	II/II	100/33	None

* Westergren erythrocyte sedimentation rate.

agnostic criteria of the American Rheumatism Association were studied. All patients had rheumatoid factor and had had active disease for at least six months, as defined by (*a*) a Westergren erythrocyte sedimentation rate (WESR) greater than 28 mm/hr., (*b*) more than six painful or tender joints, (*c*) more than three swollen joints, and (*d*) morning stiffness for more than 45 minutes. All patients were continued on a basic program of aspirin or non-steroidal anti-inflammatory medication (which was kept stable for at least six weeks) and a stable dose of corticosteroids (equivalent to no more than 10 mg of prednisone daily). No patient had been treated with intramuscular gold, penicillamine, hydroxychloroquine, azathioprine, or methotrexate during the six months prior to the study. One patient had been treated with intramuscular aurothioglucose, which was discontinued as ineffective. Patients with significant skin or kidney disease were excluded.

Following qualification for the study, each patient was started on 6 mg of auranofin daily, which was adjusted upward or downward depending on efficacy and toxicity. Patients were examined monthly, with particular attention to the WESR, number of painful, tender, or swollen joints, duration of morning stiffness, grip strength, and walking time. Both the patient's and physician's assessment regarding the efficacy of the drug were also evaluated.

Three patients are presently continuing in the study and have received the drug for 27 to 30 months (*Table 2*). All noted marked improvement in morning stiffness and joint pain, with a concomitant improvement in WESR. None experienced significant toxicity. Two patients remain on 6 mg daily and the third is currently receiving 9 mg.

Reasons for terminating the study in the 8 remaining patients are summarized (*Table 3*). Two patients appeared to show improvement, but left the area and were transferred to another investigator. In three cases, the study was terminated due to lack of effectiveness; 1 of them was unable to take more than 3 mg daily because of persistent diarrhea. (Four additional patients experienced diarrhea, which was mild, intermittent, and readily managed.) Three patients had intercurrent illness which necessitated discontinuation of auranofin. One 51-year-old man who had received the drug for 22 months was in clinical and laboratory remission at the time of the development of metastases from an unknown primary site which the investigator believed to be unrelated to the drug. Another patient, a 56-year-old woman, had received auranofin for nine months when Coombs'-positive hemolytic anemia devel-

Table 3. Cleveland Clinic experience: patients discontinuing auranofin

Patient No.	Age (yr) and Sex	Duration of Auranofin (mos)	Reason for Withdrawal
4	29F	9	Moved; transferred to another investigator
5	54F	16	Moved; transferred to another investigator
6	63F	6	Ineffective
7	73F	23	Ineffective; patient unable to tolerate 6-mg dose because of diarrhea
8	54M	13	Ineffective
9	51M	22	Unrelated malignancy; drug effective
10	56F	9	Possibly related hemolytic anemia; drug ineffective
11	22F	3	Hematochezia; drug possibly effective

oped. Although she was taking several other medications, the investigator believed that the anemia could be related to the auranofin, and it was discontinued. The third patient, a 22-year-old woman, had been on the drug for only three months and appeared to demonstrate significant early suppression of her arthritis, when hematochezia developed. Upper GI and barium-enema examinations were normal. The investigator believed that the hematochezia may have been related to auranofin. Altogether, then, of the 9 patients available for long-term study, 3 (33%) are still taking auranofin and responding well, 3 (33%) were withdrawn after 6 to 23 months when the drug proved ineffective, 2 (22%) were withdrawn because of possible drug toxicity, and 1 (11%) was withdrawn because of the development of presumably unrelated malignancy.

Worldwide experience with auranofin

To date, more than 4,000 patients have been treated with auranofin worldwide. Approximately 500 have taken it for more than three years. Wenger et al[20] reported a six-month multicenter double-blind study of 340 patients with adult-onset rheumatoid arthritis, comparing auranofin with a placebo. All of the patients were taking a basic salicylate or newer nonsteroidal anti-inflammatory drug and were treated for six months. Auranofin was significantly better than the placebo in producing marked or moderate improvement as assessed by the treating physician; moreover, there was no significant difference between the placebo and auranofin groups with regard to dropouts due to toxicity, suggesting that auranofin was tolerated well by the patients.

Several studies have compared auranofin and gold sodium thiomalate. Smith et al[21] conducted an open, random study of 52 patients and found that those treated with gold sodium thiomalate responded more rapidly, though efficacy was approximately equal at 12 months. The sedimentation rate was significantly reduced by intramuscular gold but not by auranofin. All patients withdrawn because of toxicity were in the thiomalate group. In another prospective, controlled, double-blind multi-center trial, a placebo, auranofin, and gold sodium thiomalate were compared in 193 patients with active rheumatoid arthritis.[22] A total of 161 patients completed at least 20 weeks of treatment. Significant relief of pain and tenderness (compared to the placebo) was demonstrated for both gold treatment groups, and physician assessment of disease activity improved as well. No statistical difference between the two gold groups was demonstrated in terms of clinical parameters, and the only statistically significant advantages of gold sodium thiomalate over auranofin were increased hemoglobin concentration and decreased thrombocytosis. Withdrawals because of adverse effects were five times more frequent with gold sodium thiomalate, as has been observed in all studies comparing auranofin and intramuscular gold.

An effect on radiographic progression of disease is an important characteristic of so-called "remittive" drugs. Gofton and O'Brien[23] compared the annual rate of erosions in patients on auranofin versus a placebo at 12 and 24 months of therapy, as well as to the rate of development of erosions before the introduction of auranofin. Auranofin significantly decreased the rate of erosions in comparison to both the placebo and the rate prior to therapy. Auranofin and gold sodium thiomalate were roughly comparable in effect.

Felix-Davies et al[24] compared auranofin (6 mg/day) with D-penicillamine (500 mg/day) and demonstrated equal clinical effectiveness. Reductions in the level of rheumatoid factor and the sedimentation rate were significant only in the penicillamine group. However, withdrawals from therapy were twice as common in the penicillamine group.

Experience is limited with regard to substitution of auranofin in patients who have been forced to discontinue intramuscular gold because of toxicity. Available data suggest that some patients who have had an adverse reaction to intramuscular gold may tolerate auranofin.[25] However, toxicity with both agents may be the same. Experience in patients who have done well with intramuscular gold and subsequently been switched to auranofin is also limited, though in general no clinical deterioration has been observed.[26]

The most common site of auranofin toxicity is the gastrointestinal tract.[10] Diarrhea is seen in approximately 40% of patients, most often during the first three months of therapy, but is usually manageable and accounts for withdrawal in only 3% of cases. Thirty percent of patients experienced cutaneous side effects, including a rash, pruritis, or alopecia; again this is usually mild and has resulted in discontinuation of the

drug in only 4% of patients. Stomatitis may be seen in 10% to 12% of patients, resulting in a 1% withdrawal rate. Proteinuria has been seen in 3% of patients treated with auranofin, and 0.5% have been withdrawn from therapy for this reason (significantly less than the 2% to 3% seen with intramuscular gold). The incidence of thrombocytopenia in auranofin-treated patients is 0.5%, which again is less than the 2% to 3% seen with gold sodium thiomalate or the 8% reported with penicillamine in some series.[27]

Conclusion

Auranofin appears to be unique in terms of not only its structure and pharmacokinetics, but also its potential mechanisms of action. Clinically, it could offer several advantages over intramuscular gold for the management of rheumatoid arthritis, in terms of ease of administration, diminished dropout rate, and potentially less significant toxicity despite comparable effectiveness. Many patients currently receiving intramuscular gold could be switched to auranofin.

Daniel J. Mazanec, M.D.
Department of Rheumatic Disease
The Cleveland Clinic Foundation
9500 Euclid Ave.
Cleveland OH 44106

References

1. Rodnan GP, Benedek TG. The early history of antirheumatic drugs. Arthritis Rheum 1970; **13:**145–165.
2. Lande K. Die gunstige Beeinflussung schleichender Dauerinfekte durch Solganol. Münch Med Wochenschr 1927; **74:**1132–1134.
3. Forestier J. Rheumatoid arthritis and its treatment by gold salts: results of 6 years experience. J Lab Clin Med 1935; **20:**827–840.
4. Ellman P, Lawrence JS, Thorold GP. Gold therapy in rheumatoid arthritis. Br Med J 1940; **2:**314–316.
5. The Research Subcommittee of the Empire Rheumatism Council. Gold therapy in rheumatoid arthritis. Final report of a multicentre controlled trial. Ann Rheum Dis 1961; **20:**315–333.
6. Sigler JW, Bluhm GB, Duncan H, Sharp JT, Ensign DC, McCrum WR. Gold salts in the treatment of rheumatoid arthritis. A double-blind study. Ann Intern Med 1974; **80:**21–26.
7. The Cooperating Clinics Committee of the American Rheumatism Association. A controlled trial of gold salt therapy in rheumatoid arthritis. Arthritis Rheum 1973; **16:**353–358.
8. Rothermich NO, Philips VK, Bergen W, Thomas MH. Followup study of chrysotherapy. Arthritis Rheum 1979; **22:**423–425.
9. Tepperman K, Finer R, Donovan S, et al. Intestinal uptake and metabolism of auranofin, a new oral gold-based antiarthritis drug. Science 1984; **225:**430–431.
10. Blodgett RC, Heuer M, Pietrusko RG. Auranofin: a unique oral chrysotherapeutic agent. Semin Arthritis Rheum 1984; **13:**255–273.
11. Walz DT, DiMartino MJ, Chakrin LW, Sutton BM, Misher A. Antiarthritic properties and unique pharmocologic profile of a potential chrysotherapeutic agent. SK&F D-30162. J Pharmacol Ther 1976; **197:**142–152.
12. Walz DT, DiMartino MJ, Griswold DE, Intoccia AP, Flanagan TL. Biologic actions and pharmacokinetic studies of auranofin. Am J Med 1983; **75:**30:90–108.
13. DiMartino MJ, Waltz DT. Inhibition of lysosomal enzyme release from rat leukocytes by auranofin. A new chrysotherapeutic agent. Inflammation 1977; **2:**131–142.
14. Wolach B, DeBoard JE, Coates TD, Baehner RL, Boxer LA. Correlation of in vitro and in vivo effects of gold compounds on leukocyte function: possible mechanisms of action. J Lab Clin Med 1982; **100:**37–44.
15. Kleine L, Buckendorf K, Herrlinger JD. The influence of nonsteroidal anti-inflammatory drugs and gold salts on human monocyte function in vitro. [In] Proceedings of the 15th International Congress of Rheumatology. New York, Academy Professional Information Services, 1982, pp 75–77.
16. Davis P, Johnston C, Miller C, Wong K. The effect of gold compounds on the respiratory burst of phagocytic cells (abst). Arthritis Rheum 1982; **25:**S131.
17. Walz DT, Griswold DE. Immunopharmacology of gold sodium thiomalate and auranofin (SK&F D-39162). Effects on cell-mediated immunity. Inflammation 1978; **3:**117–128.
18. Lorber A, Jackson WH, Simon TM. Assessment of immune response during chrysotherapy. Comparison of gold sodium thiomalate vs auranofin. Scand J Rheumatol 1981; **10:**129–137.
19. Walz DT, DiMartino MJ, Griswold DE. Immunopharmacology of auranofin and gold sodium thiomalate: effects of humoral immunity. J Rheumatol 1979; **6**(Suppl 5):74–81.
20. Wenger ME, Alexander S, Bland JH, Blechman WJ. Auranofin versus placebo in the treatment of rheumatoid arthritis. Am J Med 1983; **75:**123–132.
21. Smith PR, Brown GMM, Meyers OL. An open comparative study of auranofin vs gold sodium thiomalate. J Rheumatol 1982; **9**(suppl 8):190–196.
22. Ward JR, Williams HJ, Egger M, et al. Comparison of auranofin, gold sodium thiomalate, and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. Arthritis Rheum 1983; **26:**1303–1315.
23. Gofton JP, O'Brien WM. Effects of auranofin on the radiological progression of joint erosion in rheumatoid arthritis. J Rheumatol 1982; **9**(suppl 8):169–172.
24. Felix-Davies DD, Stewart AM, Wilkinson BR, Bateman JR, Delamere JP. A 12-month comparative trial of auranofin and D-penicillamine in rheumatoid arthritis. Am J Med 1983; **75:**138–141.
25. Personal communication. Research and Development Division, Smith Kline and French Laboratories.
26. Wenger ME, Bernhard GC, Heller MD. Therapy for rheumatoid arthritis: transferring treatment from injectable gold to auranofin. [In] Capell HA, Cole DS, Monghoni KK, eds. Auranofin: Proceedings of a Smith Kline & French International Symposium. Amsterdam, Excerpta Medica, 1983, pp 201–210.
27. Halverson PB, Kozin F, Bernhard GC, Goldman AL. Toxicity of penicillamine. A serious limitation to therapy in rheumatoid arthritis. JAMA 1978; **240:**1870–1871.