Complications of Gold Therapy and Their Management

WILLIAM C. KUZELL, M.D., *San Francisco*

SUMMARY

Early recognition of manifestations of gold intoxication is important to the treatment of such complications. Proper dosage schedules should be followed and blood and urine frequently examined.

Most toxic manifestations subside, but those which become worse or which do not subside on withdrawal of the gold should be treated with BAL (2, 3-Dimercaptopropanol).

BAL has a toxicity of its own and is painful on injection. Since BAL combines with gold, the therapeutic effect of the metal may be lost after such treatment.

The beneficial effects of methionine and methionine plus BAL in treatment of experimentally induced gold intoxication of animals suggests such combined therapy in the treatment of clinical complications of gold poisoning. A schedule of combined antidotes is outlined.

WHILE polypharmacy is still the rule in the treatment of rheumatoid arthritis, many physicians advocate the therapeutic use of gold as the medicament of choice.[3, 10, 18, 20] As no causative agent has been isolated, the use of gold in this disease is purely empiric (stemming largely from extensive use of the metal by Forestier[9] 20 years ago) but this form of treatment is evidently here to stay until some better or more rational therapy is developed. Unfortunately, gold like other heavy metals and metalloids must be used with considerable caution due to its toxicity.

The purpose of this presentation is to outline the toxic complications of gold therapy and the management of them. Six case reports are included to illustrate the course and management of gold intoxication.

TOXIC COMPLICATIONS

The toxic complications of gold therapy may be divided into two general categories: (1) initial hypersensitivity reactions, and (2) cumulative toxic manifestations. There is no good evidence that hypersensitivity reactions following the use of gold are more common than those following use of other metals and metalloids. These hypersensitivity reactions include rapid decrease in leukocytes with the development of agranulocytosis and decrease in platelets with the development of purpura. Comroe[5] mentions the occurrence of a "true anaphylactic" reaction following the injection of gold, but true sensitization has not been demonstrated experimentally. Soluble gold salts are rapidly reduced to the metallic state which is poorly absorbed. Sollmann[21] suggests that the immediate reactions of a vasomotor character, presumably after intravenous injection, may be due to flocculation of the reduced gold. Minute particles of metallic gold have been demonstrated in the kidneys, spleen, and liver of animals treated with gold sodium thiosulfate intramuscularly, but without immediate systemic reaction.[14]

In general the reactions of most concern to the clinician are those which occur after the injection of a total of 0.4 to 0.8 gm. of a gold salt. These reactions include cutaneous erythema, generalized itching, scaling dermatitis of the eyelids (Case 6), exacerbations of fungus infections of the skin (Case 3), chronic herpetic infections, the development of small furuncles (Case 4), and pruritic papular eruption (Case 2). An extremely rare manifestation is the development of chrysiasis, which is a permanent discoloration of the skin following the extended use of gold. This is comparable to discoloration after the prolonged use of silver salts. The oral manifestations include metallic taste, ulcerative stomatitis (Case 1), sore tongue and loss of taste. The gastrointestinal manifestations include nausea, occasional vomiting and epigastric distress, hiccough, diarrhea, and, rarely, ulcerative enteritis. The renal manifestations include albuminuria, hematuria, and uremia. Now and then, late in the course of medication, there is transitory glycosuria.

Occasionally a patient may report precordial discomfort, and not infrequently following the first few injections of gold there is a slight fever for 24 to 36 hours together with an exacerbation of joint pains and stiffness. After five or six injections these symptoms usually disappear, presumably as a result of tolerance for the gold, for it is well known that animals develop an increased tolerance for certain heavy metals when repeatedly injected. If a patient does not cease having the immediate reactions the medication should be discontinued (Case 5). During the course of medication eosinophilia occasionally makes its appearance, and if the eosinophils exceed 15 per cent it is desirable to discontinue therapy until the eosinophil count has returned to normal (Case 2). A rise in eosinophil count often precedes the development of papular dermatitis.

Hepatic manifestations of gold poisoning include jaundice and acute yellow atrophy, but these complications are rare.

The respiratory manifestations include hemo-

From the Departments of Pharmacology and Therapeutics and of Medicine, Stanford University School of Medicine.

Presented before the Northern California Rheumatism Association, October 15, 1948, San Francisco.

This work was supported, in part, by contract with the Office of Naval Research, United States Navy, and in part by the Stern Fund for Arthritis Research.

ptysis, epistaxis and cough, but these also are infrequent.

From the listing of so many toxic possibilities the impression may be gained that perhaps many observers have ascribed to gold salts toxic manifestations which are not entirely due to the gold. Competent workers in the field of rheumatic diseases report principally dermatitis and stomatitis as toxic manifestations and less commonly exfoliative dermatitis and purpura, and even more rarely, agranulocytosis. Aplastic anemia has occasionally been reported, but oftentimes other medication may have been responsible. Cecil[3] noted toxic reactions in 42 per cent of 245 cases, which may be broken down as follows: skin reactions, 52 cases; gastrointestinal symptoms, 18 cases; stomatitis, 13 cases; exfoliative dermatitis, 11 cases; purpura and marked albuminuria, three each; jaundice and bronchitis, two each; and agranulocytosis, one case. Other clinicians report different percentages depending on the product used and the dosage schedule, but the relative frequency of the reactions is about the same in all series.

There is no certain way of predicting which patients will develop toxic reactions, but there are certain conditions in which the use of gold therapy is contraindicated. These include history of agranulocytosis, purpura, disease of kidneys or liver, severe diabetes mellitus, pregnancy (gold passes through the placenta), congestive heart failure, hemophilia, severe anemia of hemorrhagic tendency, eczema, and colitis. Psoriasis, which occasionally is seen in patients with rheumatoid arthritis, is not a contraindication to gold therapy, although patients who have psoriasis do not usually respond as well as those who have uncomplicated cases. Fortunately the other disease states mentioned as contraindicative do not often occur in conjunction with rheumatoid arthritis. Many physicians are loath to use gold in the treatment of childhood rheumatoid arthritis (Still's disease) or in rheumatoid arthritis in elderly patients; however, there is no sound pharmacological evidence that the very young or the very old tolerate gold less well than others.

Some instances of death following the use of gold have been reported.[1] Such fatalities have been rare, and perhaps no more common than after the use of other heavy metals and metalloids in other conditions. Women seem to be about eight times more likely to develop gold poisoning than men.[5] This is a fact of some interest, since the principal clinical use of gold is in a disease which is three to four times more common in females than in males.

MANAGEMENT OF GOLD TOXICITY

The best way of managing the complications of gold poisoning is in preventing them by the proper administration of gold salts. A suggested course of medication using either sodium aurothiomalate (Myochrysine) or aurothioglucose (Solganol-B) is to give 10 mg. intramuscularly once weekly for three or four doses, then 25 mg. weekly to a total of 150 to 200 mg., followed by weekly doses of 50 mg. to a total dose of 1,200 to 1,400 mg. At this point, if the arthritis appears to be under control and no toxic manifestations due to gold are evident, treatment may proceed with 50 mg. given every two or three weeks until a total of 1,800 to 2,000 mg. is reached. Usually at this point the interval between injections can be increased to four to six weeks, the frequency depending upon the symptomatic response. Gold sodium thiosulfate has no known therapeutic advantage over these other water-soluble compounds, and intravenous use of the drug is, therefore, to be discouraged because of the potential danger inherent to all intravenous medication. Before and after the first injection of gold, a count of the blood cells should be made; and thereafter, every two to four weeks the blood and urine should be examined. Prior to each injection of gold the patient should be questioned carefully for any evidence of gold poisoning, including dermatitis, pruritus, purpura, stomatitis, nausea, vomiting, jaundice, and diarrhea. Liver function tests are advisable prior to gold therapy, especially if damage of the liver is suspected.

When patients under treatment with gold salts have mild toxic reactions, such as itching, small areas of papular dermatitis, mild stomatitis, transitory increase in joint symptoms, and slight fever following injections, it is not necessary or desirable to use BAL (2, 3-Dimercaptopropanol) at once. It is preferable to stop the administration of gold and observe the patient carefully for several weeks. Should the manifestations of intoxication become steadily worse, treatment with BAL should be instituted. If the signs of intoxication disappear during the interval of observation, gold may be resumed cautiously with smaller doses or sometimes a change to another preparation. If on resumption of chrysotherapy the toxic manifestations flare up again, it is probably best to abandon the use of gold for several months before trying it again. Itching may be treated with a measure of success with the antihistamine drugs—diphenhydramine, tripelennamine and the like—by mouth and in ointments; these drugs do not, however, relieve all patients of itching. Penicillin lozenges apparently alter favorably the course of mild stomatitis (Case 6).

TREATMENT WITH BAL AND METHIONINE

Formerly little could be done for the toxic manifestations of gold, once they became definite. Now, however, it has been established experimentally and clinically that the use of BAL (2, 3-Dimercaptopropanol) has considerable merit in the treatment of the toxic complications of gold salts. Gold forms a chemical complex with BAL which is precipitated out of solution *in vitro*. In patients and animals the use of BAL promotes the urinary excretion of gold, probably in a complex form, and spares the kidneys, as has been shown histologically.[4, 7, 15, 19] There is some evidence that after gold has been in the body for a long time BAL will not as readily promote excretion of it, and this may have something to do

with the physical state of the stored gold, which seems to be in a reduced insoluble form in various tissues.

Recently Gillmor and Freyberg[12] reported that, in rats, BAL had to be given simultaneously with gold to protect the renal epithelium and that BAL given after an interval of several days did not show a protective effect. However, in their investigations the animals were given excessive doses of gold. In man, on the other hand, Macleod[16] reported favorable results in the treatment of dermatitis, stomatitis, and hepatitis caused by gold. In Macleod's series of 15 cases BAL certainly altered favorably the course of the toxic reactions even though it was administered long after the gold had been first given.

BAL is not a perfect detoxicant for heavy metals, since it has a considerable toxicity of its own. MacNider[17] reported liver injury in dogs following the use of BAL in doses of 15 to 30 mg. per kg. of body weight. Graham and Hood[13] noted that BAL inhibited the action of insulin.[14] Others[8] have shown that in small animals it causes conjunctivitis, ataxia, rapid and then impaired respiration, and convulsions. In man, toxic symptoms have been noted at a dosage of 5 mg. per kg. of body weight. The symptoms included nausea, vomiting and headache, a burning sensation of the lips, mouth, throat and eyes, sometimes with accompanying lacrimation or salivation, and pain in the teeth; generalized muscular aches with burning and tingling of the extremities; and a sense of constriction in the chest with a feeling of anxiety.[22] These symptoms usually disappear in less than two hours. The injection of BAL is rather painful, and since the substance is administered intramuscularly in oil it may cause local necrosis and form a suitable nidus for bacterial growth if bacteremia is present.[2]

In view of the appreciable toxicity of BAL some less toxic compound would be desirable. Danielli[6] and associates report that BAL-glucoside may be such an agent. Also it has been shown[14] that methionine, a sulfur-containing amino-acid, added to the diet of white rats will protect the animals against lethal doses of gold sodium thiosulfate, and that, when used in combination with BAL, the protective effect is greater than when either substance is used alone. Methionine protects without increasing the excretion of gold, thus presumably blocking the toxic effects of gold by an unknown mechanism. Rats given 1 to 3 per cent methionine in their food survive lethal doses of gold sodium thiosulfate almost as well as controls treated with BAL. With doses of gold against which neither methionine nor BAL used alone will protect the animals, the combined use of these two agents permits the survival of significant numbers, females being protected to a greater extent than males. This form of combined treatment of the toxic reactions to gold has not yet been tried extensively clinically, but preliminary results showing significant reduction in mortality in animals indicate considerable promise when BAL and methionine are used concurrently.[14] As to promoting excretion of gold, use of methionine alone in four patients (other than those reported upon herein) did not do so, a result which accords with results in animals.

It is still too early to say whether patients treated with BAL for gold intoxication undergo a subsequent exacerbation of rheumatoid arthritis. It seems reasonable to expect, however, that such might be the case (Case 1). There is no reason why chrysotherapy may not be resumed subsequent to the successful treatment of minor toxic reactions. If gold therapy is resumed at a later date and gold salts are administered cautiously in smaller dosage the "control" of the arthritis may not be lost.

A regimen of treatment with BAL is suggested as follows: Inject intramuscularly 0.5 cc. of the 10 per cent suspension in oil as a test dose for BAL hypersensitivity. If no reaction occurs, follow with the administration of 0.025 cc. (2.5 mg.) per kg. of body weight at four-hour intervals for four to six injections daily during the first two days and then two injections daily for a period of ten days or until recovery. Since the injections are quite painful, 0.5 cc. of a 2 per cent procaine solution may be added. In conjunction with the BAL, 1 to 2 gm. of methionine may be given by mouth four times daily. For the treatment of exfoliative dermatitis the presence of a secondary infection of the skin must be considered, and, if possible, BAL should be injected through healthy rather than diseased or infected skin. The concurrent use of penicillin in such cases is beneficial. For control of pruritus, use of the antihistamine substances in ointments and by mouth sometimes provides a measure of temporary relief.

The following case summaries illustrate examples of gold intoxication and its management:

CASE 1: Female, aged 63. Diagnosis: rheumatoid arthritis. After receiving 0.555 gm. Solganol-B (aurothioglucose) sore throat and mouth developed, with ulceration and bleb formation. BAL was given (10 per cent suspension in oil), 0.5 cc. and 1.0 cc. on the first day and 2.0 cc. on the second day. The buccal and pharyngeal lesions were much better on the second and third days and on the fourth day there was no visible ulceration other than a small healing ulcer on the under surface of the upper lip. After the last injection of BAL the patient had a "terrible headache" during which "even the individual teeth ached." The headache disappeared in several hours. A week later the joint pains returned. Two weeks later the joint pains were more severe and the left buttock was still tender at the site of the BAL injections. Three weeks later the patient was given Solganol-B, 25 mg. intramuscularly, and by the fourth week the joint pain had become much less severe. The blood cell count was not abnormal before, during, or after this toxic episode.

CASE 2: Female, aged 31. Diagnosis: Rheumatoid arthritis. After ten injections of Solganol-B, to a total dose of 0.305 gm., itching in the ears and some rash on the neck, right hand, left thigh, and under the breasts were noted. Tripelennamine (2 per cent) ointment was applied and the gold was discontinued. Fourteen days later the joints were almost asymptomatic and the rash about the same. One week later the rash was three to four times more extensive. The ointment reduced the itching temporarily, but BAL therapy was begun with 0.5 cc. and 1.0 cc. the first day and

2.0 cc. the second day. A week later the dermatitis was even more extensive with considerable exudate. BAL was again given (2.0 cc.) and the following day repeated. The patient vomited one hour after the second injection. A week later the dermatitis was again worse and 1.0 cc. of BAL was given. Anti-histamine agents by mouth did not materially reduce the itching. The following day 2.0 cc. BAL and 300,000 units of penicillin in oil were administered. The patient was given methionine 3.0 gm. daily by mouth for two weeks. BAL was then given daily in a 2.0 cc. dosage for three more days and the skin lesions began to clear and the itching was considerably decreased. One month after the last dose of BAL the skin lesions were dry, and discolored areas showed no crusts or exudates; the only itching was under the breasts. There was no recurrence of the arthritis. Two weeks prior to the onset of the dermatitis, examination of the patient's blood had shown 5,600 leukocytes per cu. cc. with 9 per cent eosinophils, whereas two months before there had been only 2 per cent eosinophils in 4,900 leukocytes.

CASE 3: Male, aged 50. Diagnosis: Rheumatoid arthritis. One day after an initial injection of 10 mg. Solganol-B, pronounced exacerbation of epidermophytosis of the hands and feet developed, as well as severe headache and conjunctivitis. The epidermophytosis and epidermophytid reactions subsided slowly in a period of three weeks. No more gold was administered.

CASE 4: Male, aged 44. Diagnosis: Rheumatoid arthritis. The patient, who was on a maintenance dose of 50 mg. of Solganol-B per month, began to have arthritic symptoms. The dosage was increased to 50 mg. per week for five doses, after which folliculitis of the left axilla developed. A week later another 50 mg. of Solganol-B was given and the folliculitis evolved to furunculosis. Gold was discontinued and after two daily injections of 300,000 units of penicillin in oil the furunculosis began to improve. A month later the joint pains returned. Solganol-B, 25 mg., was given and the skin lesions did not return and the joint pain subsided. A dosage of 25 mg. every three to four weeks was continued, with relief of joint pain and no recurrence of toxic symptoms.

CASE 5: Male, aged 27. Diagnosis: Rheumatoid arthritis. After the first injection of 10 mg. of Solganol-B the patient reported exacerbation of all arthritic pains within a few hours of the injection. Generalized itching also developed, but no rash. The same type of reaction followed each of five injections of 10 mg. of Solganol-B. On several occasions the patient had a low-grade fever for 36 hours following the injections. Dosage was reduced to 5 mg. and the same reaction occurred. Two injections of 10 mg. of Myochrysine at weekly intervals were given and the same reaction followed. After four more 10 mg. injections of Solganol-B at weekly intervals, therapy was abandoned, since the reactions were too severe in the 24- to 36-hour periods thereafter. During this time there was no change in the blood picture.

CASE 6: Female, aged 53. Diagnosis: Rheumatoid arthritis. The patient often complained of soreness of the mouth for 24 hours following weekly injections of Solganol-B, but there were no lesions of the buccal mucosa until the total dose was 0.45 gm. Penicillin troches used every two hours during the day caused prompt improvement in the lesions. A week following another 50 mg. dose of Solganol-B, a white lesion 2 mm. in diameter appeared on the inner surface of the upper lip. Two weeks later 25 mg. of Solganol-B was given and the mouth was healed; however, after that injection some itching of the right upper eyelid developed. During the next month the patient was given weekly injections of 25 mg. each and during the month herpes on the lower lip developed, but there were no visible skin lesions. Finally after another 25-mg. injection and then a 12-mg. injection, scaling dermatitis of the eyelids developed—this after a total dose of 0.662 gm. No more gold was given. Neo-antergan (pyranisamine maleate) 50 mg., taken orally at four-hour intervals, gave some relief of the itching. During a three-month follow-up period without gold the skin lesions cleared completely and the joint pains did not return. Neither BAL nor methionine was used to combat the manifestations of gold intoxication in this case.

REFERENCES

1. Anderson, N. L., and Palmer, W. L.: The danger of gold salt therapy—Report on fatal case, J.A.M.A., 115: 1627-1630 (Nov. 9), 1940.

2. Carleton, A. B., Peters, R. A., and Thompson, R. H. S.: The treatment of arsenical dermatitis with Dimercaptopropanol (BAL), Quart. J. Med., New Series No. 65:49-79 (Jan.), 1948.

3. Cecil, R. L.: A Textbook of Medicine, ed. 7, Philadelphia, W. B. Saunders Company, 1947.

4. Cohen, A., Goldman, J., and Dubbs, A. W.: The treatment of acute gold and arsenic poisoning, J.A.M.A., 133: 749-752 (March 15), 1947.

5. Comroe, B. I.: Arthritis and Allied Conditions, ed. 3, Philadelphia, Lea and Febiger, 1947.

6. Danielli, J. F., Danielli, M., Mitchell, P. D., Owen, L. N., and Shaw, G.: Development of chemotherapy for systemic arsenical poisoning, Nature, London, 157:217-218 (Feb. 23), 1946.

7. Davison, R.: BAL therapy of dermatitis caused by injections of gold salts, Stanford Med. Bull., 5:37-39 (Feb.), 1947.

8. Durlacher, S. H., Bunting, H., Harrison, H. E., Ordway, N. K., and Albrink, W. S.: The toxicological action of 2, 3-Dimercaptopropanol (BAL), J. Pharm. & Exp. Therap., 87:Suppl. 28-32 (August), 1946.

9. Forestier, J.: Rheumatoid arthritis and its treatment by gold salts: The results of six years' experience, J. Lab. and Clin. Med., 20:827-840 (May), 1935.

10. Fraser, T. N.: Gold treatment in rheumatoid arthritis, Ann. Rheum. Dis., 4:71-75 (June), 1945.

12. Gillmor, C. S., and Freyberg, R. H.: The effect of 2, 3-Dimercaptopropanol (BAL) on gold toxicity in rats, J. Lab. Clin. Med., 33:1024-1028 (August), 1948.

13. Graham, J. D. P., and Hood, J.: Actions of British Anti-Lewisite (2, 3-Dimercaptopropanol), Brit. J. Pharmacol. and Chemotherapy, 3:84-90 (March), 1948.

14. Kuzell, W. C., Gardner, G. M., Meyer, D. L., and Tripi, H. B.: Methionine and 2, 3-Dimercaptopropanol (BAL) in acute toxicity of gold sodium thiosulfate, Stanford Med. Bull., 7:65-69 (May), 1949.

15. Kuzell, W. C., Pillsbury, P. L., and Gellert, S. A.: The effects of 2, 3-Dimercaptopropanol (BAL) on toxicity and excretion of gold, Stanford Med. Bull. 5:197-202 (Nov.), 1947.

16. Macleod, J. G.: BAL in the treatment of gold toxicity, Ann. Rheum. Dis., 7:143-151 (Sept.), 1947.

17. MacNider, W. deB.: Liver injury in the dog following use of 2, 3-Dimercaptopropanol (BAL), Proc. Soc. Exp. Biol. and Med., 66:444-446 (Nov.), 1947.

18. Ragan, C., and Tyson, T.: Chrysotherapy in rheumatoid arthritis, Am. J. Med., 1:252-256 (Sept.), 1946.

19. Ragan, C., and Boots, R. H.: The treatment of gold dermatitides, J.A.M.A., 133:752-753 (March 15), 1947.

20. Rawls, W. B., Gruskin, B. J., Ressa, A. A., Dworzan, H. J., and Schreiber, D.: Analysis of results obtained with small doses of gold salts in the treatment of rheumatoid arthritis, Am. J. Med. So., 207:528-533 (April), 1944.

21. Sollmann, T.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, ed. 7, Philadelphia and London, W. B. Saunders Co., 1948.

22. 2, 3-Dimercaptopropanol in oil, new and nonofficial remedies, J.A.M.A., 137:363 (May 22), 1948.