Nitritoid Reactions: Case Reports, Review, and Recommendations for Management

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ABSTRACT. ***Objective.*** We assessed nitritoid reactions, which are a well recognized side effect of chrysotherapy that occur in roughly 5% of patients taking gold sodium thiomalate (GST).

Methods. Between January 1996 and January 2000, 8 patients followed in our gold monitoring program at Mary Pack Arthritis Centre experienced nitritoid reactions observed by the clinic nurse. We undertook a chart review to determine the risk factors, timing, course, and outcome of nitritoid reactions.

Results. Patients' ages ranged from 36 to 69 years, and 7 of 8 were women. Duration of gold therapy prior to nitritoid reactions ranged from 13 months to 13 years. Seven had previously had mucocutaneous reactions, and one experienced gold dermatitis following a nitritoid reaction. Two of 8 patients were taking angiotensin converting enzyme inhibitor agents. Seven reactions were classified as mild, and one was a severe reaction with hypotension, syncope, and angina.

Conclusions. Management includes a high index of suspicion in patients experiencing nausea, flushing, or dizziness following gold injections, switching from GST to gold sodium aurothioglucose, injection in the recumbent position, and observation for 20 minutes after injections in individual patients. (J Rheumatol 2001;28:2209–12)

Key Indexing Terms:

ANTIRHEUMATIC DRUGS
GOLD SODIUM AUROTHIOMALATE
GOLD SODIUM AUROTHIOGLUCOSE
ADVERSE EFFECTS
CHRYSOTHERAPY
NITRITOID REACTIONS

Nitritoid reactions are a well recognized side effect of chrysotherapy. The typical episode includes facial flushing and dizziness. Nausea, vomiting, and symptoms of hypotension, including syncope, may be experienced. Characteristically, these reactions are transient, occurring within minutes of drug administration[1,2]. Serious sequelae have been reported, including myocardial infarction and stroke[3-7].

At the Mary Pack Arthritis Centre, a drug monitoring program for injectable gold has operated for 30 years. About 50 new patients are referred annually for education, medication administration, drug monitoring, and self-injection education. In 1997, we observed for the first time a serious nitritoid reaction in a patient whose milder reactions had been missed and misunderstood. This led us to review our experience with nitritoid reactions in the clinic, to review the literature concerning nitritoid reactions, and to propose guidelines for management.

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MATERIALS AND METHODS

Records of all patients seen in the gold clinic between January 1996 and January 2000 were reviewed to evaluate instances of nitritoid reactions, onset in relationship to initiation of gold, dose of medication, patient and disease characteristics, management, and outcomes of reactions. A literature search using MeSH terms nitritoid reactions, vasomotor reactions, gold, chrysotherapy, gold sodium aurothiomalate, gold sodium aurothioglucose (ATG), myochrysine, and solganal was performed, and the manuscripts reviewed to determine the experience of others. Based on this information, clinic staff developed a protocol that permits recognition and management of nitritoid reactions.

The gold treatment regimen consists of weekly injections beginning with the test dose of 10 mg, followed by 25 mg, and subsequently 50 mg weekly. Thereafter, the regimen is predominantly a weekly injection schedule of 25 or 50 mg, depending on tolerability. Once the patient achieves the expected response or remission, the gold may be reduced to every 2 weeks. In the event of a sustained gold induced remission, intervals between injections may be gradually increased to monthly. If improvements in clinical and laboratory outcomes, and in reduced erosions, are not achieved on a biweekly regimen, weekly injections may be continued as maintenance therapy[8]. If there is a partial response to weekly gold, a second disease modifying antirheumatic drug is commonly added. In the event of a side effect that is not serious, gold is held back until the side effect subsides, and then resumed at a 50% lower dosage. About 20% of our patients do not tolerate standard doses of gold, and in these patients we reduce the dose by 50% sequentially until a dose is reached to which the patient does not develop reactions[9]. Over time, many patients are desensitized to the mucocutaneous side effects, and the dose of gold can be adjusted gradually upwards if needed to control rheumatoid arthritis (RA).

Gold is not normally discontinued except for lack of effect after an adequate trial, or in the event of potentially serious side effects, such as thrombocytopenia, aplasia, pulmonary infiltration, hepatitis, or enterocolitis. Mucocutaneous effects of gold, such as dermatitis and stomatitis, are so common that the protocol allows the nurse to make needed adjustments

on a week by week basis, and the physician evaluates the patient every 3 to 6 months, and more frequently when needed. Proteinuria ≥ 500 mg/dl normally requires temporary discontinuation of gold. Once proteinuria has subsided, gold is reintroduced at 50% lower dosage[10]. In patients who stop and restart gold, we have designated a second course when intervals between injections are 8 months or longer[11].

A nitritoid reaction is diagnosed based on the presence of flushing observed by the clinic nurse or physician following a gold injection, and any one of the following associated symptoms: weakness, dizziness, nausea, vomiting and patient reports feeling faint, or syncope.

RESULTS

Between 1996 and 2000, 8 gold-treated patients followed in the gold clinic experienced nitritoid reactions. During this period, the average clinic caseload was 270 patients, but there were admissions and discharges that make an actual incidence difficult to calculate. Of these patients, roughly two-thirds received gold sodium thiomalate (GST). At 2 incidents per year, nitritoid reactions were an uncommon side effect in our clinic. Details of patient characteristics and gold treatment are summarized in Table 1. There were 8 patients with RA (7 female, one male), age 36 to 69 years. Duration of gold therapy prior to the first nitritoid reaction ranged from 13 months to 13 years. One patient was receiving a second course of gold treatment, and one patient was receiving a third course. Seven/eight patients had previously experienced mild mucocutaneous reactions to gold, whereas one patient (Patient 8) developed a mild generalized pruritic gold dermatitis 8 weeks after a nitritoid reaction. Mucocutaneous side effects were managed effectively in all 8 patients by interruption of therapy and careful dose adjustment. At the time of the nitritoid reaction, the total cumulative dosage of gold ranged from 1375 to 7685 mg counting only the current gold course. All patients were receiving weekly GST injections at a dose of 25 to 50 mg. In 7 of 8 cases, reactions lasted 10 minutes or less with no sequelae. In 7 of 8 patients, reactions occurred within seconds to 5 minutes, and in one patient, onset was recognized 10 minutes after injection. One patient experienced a severe reaction including hypotension, prolonged syncope, and angina (described in detail below). In 2 patients, the first nitritoid reaction occurred at intervals of 1–4 weeks after starting angiotensin converting enzyme (ACE) inhibitors for management of hypertension.

In our patients, management following nitritoid reactions included dose reduction by at least 50% in 6/8 patients without recurrence of reactions. Two patients who had been

Table 1. Patient characteristics and treatment.

Patient	Age, yrs	Duration of RA, yrs	Duration of Gold Prior to Reaction	Gold Schedule Prior to Reaction	Severity of Reaction	Gold Schedule After Reaction	Response to Gold Therapy
1	38	5	13 mo	GST 45 mg weekly	Mild	No change in gold preparation or dose	No further reactions; followup 29 mo; RA well controlled
2	69	16	13 yrs	GST 50 mg weekly	Severe	Refused further gold therapy	RA in remission; no treatment
3	40	3	3 yrs	GST 30 mg weekly	Mild	Decreased GST to 15 mg weekly; dose increased slowly; usual dose resumed 3 weeks after NR	No further reactions; followup 28 mo; RA well controlled
4	36	3	27 mo	GST 25 mg weekly	Mild	GST 10 mg weekly; usual dose resumed 16 weeks after NR	No further reactions; followup 19 mo; RA well controlled
5*	49	11	24 mo 2nd course	GST 40 mg weekly	Mild	Switched to ATG 25 mg weekly; dose increased slowly; usual dose resumed 6 weeks after NR	No further reactions; followup 18 mo; RA slightly more active
6	44	8	15 mo	GST 50 mg weekly	Mild	Switched to ATG 25 mg weekly; dose increased slowly; usual dose resumed 16 weeks after NR	No further reactions; followup 7 mo; RA improved
7	44	13	17 mo 3rd course	GST 50 mg weekly	Mild	Switched to ATG 10 mg weekly; dose increased slowly; usual dose resumed 20 mo after NR	No further reactions; followup 42 mo; RA more active
8*	52	16	13 yrs	GST 50 mg weekly	Mild	Switched to ATG 10 mg; usual dose resumed 4 weeks after NR	No further reactions; followup 9 mo; RA well controlled

* Denotes patient taking ACE inhibitor. GST: gold sodium aurothiomalate (Myochrysine); ATG: gold sodium aurothioglucose (Solganal); NR: nitritoid reaction.

receiving ACE inhibitors were switched to ATG. In Patient 1, who had experienced a mild reaction, there was no change to the gold preparation or the dose, with no further problems over a followup period of 29 months. No patient experienced a recurrence of nitritoid reactions after a mean followup of 22 months.

CASE REPORTS

Case 1: A severe nitritoid reaction. Patient 2, a 69-year-old woman, was referred to the gold clinic in 1983 with a one year history of seropositive erosive RA. She had an excellent response to GST; erythrocyte sedimentation rate fell from 90 to 20 mm/h in the first year, and with continuous weekly injections for 2 years she obtained a complete remission. Gold was reduced to injections every 3–4 weeks, and the remission was sustained. In 1996, she volunteered for a clinical trial of gold discontinuation, and received placebo for 5 months before symptoms of RA reemerged. In May 1996, she resumed GST 50 mg weekly. Between May 1996 and February 1997, she attended clinic weekly. At each clinic visit, the nurse inquired about reactions to gold; none were reported or observed. In February 1997, she was feeling unwell, and was given hydrochlorothiazide 25 mg for hypertension. She did not come to the clinic for 4 weeks. On March 7, she developed a severe nitritoid reaction in the clinic minutes after receiving GST. She had facial flushing, loss of consciousness for 3 minutes, and angina. Her systolic blood pressure at the time was 40 mm Hg. The entire episode lasted 20 minutes. When she regained consciousness, she provided a history of feeling lightheaded about 20 minutes after gold injections for about 5 months prior, and one episode of fainting while returning home after a gold injection. None of these reactions had been observed by a health professional. She had not taken them seriously, and had not reported them to the nurse or physician. At the time nitritoid reactions first developed, she had received a total cumulative dose of 7685 mg of gold over a period of 13 years. Because of the frightening nature of this severe nitritoid reaction, she refused further gold therapy. She attended her family doctor for regular followup, but did not return to the gold clinic. When contacted one year later by telephone, she reported that her RA was under control with no treatment.

Case 2: A nitritoid reaction following initiation of ACE inhibitor therapy. Patient 8 was a 52-year-old man with seropositive RA who had received GST between 1987 and 1992, and combination gold and methotrexate between 1992 and 1999 without incident. In 1999, he had 2 myocardial infarctions, and was prescribed ACE inhibitor therapy (ramipril). In January 2000, he experienced facial flushing, marked conjunctival injection, sweating, and lightheadedness within a few minutes after receiving 50 mg GST. The episode lasted 5 minutes. He was switched to the following schedule of ATG: 10, 25, and 50 mg weekly. After 2 months, he developed a mild pruritic gold dermatitis. The gold was held back temporarily, and resumed at 50 mg every 2 weeks once the rash resolved.

DISCUSSION

Nitritoid reactions occur in roughly 5% of patients treated with GST[12,13]. Ho and Pullar claim that such reactions usually occur early in the course of gold, but may develop in patients long established on gold therapy[1]. There are case reports of late appearing nitritoid reactions. Davison described experience with 3 nitritoid reactions occurring at 6 months, 8 years, and 2.5 years[14]. The latter patient had received a prior course of GST for 9 years without problems. Healey and Backes describe late appearing nitritoid reactions in 4 patients, all of whom had recently been prescribed ACE inhibitors[15]. Management included discontinuation of ACE inhibitors in 2 patients, switching from GST to ATG in one patient, and dose reduction of GST in one patient. Hill, *et al*[16], Karrar, *et al*[17], and Ching and McClintock[18] each describe one patient who developed nitritoid reactions while taking ACE inhibitors, although the time course of development of reactions in relation to prescription of ACE inhibitors did not prove a relationship. One of those described by Ching and McClintock resembles our Patient 8. Sixteen months after starting GST, and 12 months after starting lisinopril, their patient experienced a severe nitritoid reaction with hypotension and loss of consciousness; she recovered with cardiopulmonary resuscitation, adrenaline, and hydrocortisone. That patient had a sustained remission of RA and was treated subsequently with hydroxychloroquine. A 71-year-old woman described by Tilelli and Heinrichs developed a nitritoid reaction while receiving GST and captopril[3]. She was switched to ATG, with no recurrence of nitritoid reactions. Fourteen weeks later, while in hospital for a minor surgical procedure, she was given GST because the hospital did not carry ATG in the formulary. She developed a severe nitritoid reaction, lost consciousness, and died. A computer tomographic scan of the brain revealed ischemic changes. The authors cautioned that "parenteral gold preparations differ in their suspensory vehicles and bioavailability, and should not be considered generic equivalents"[3].

Nitritoid reactions occur primarily in patients treated with GST, but there are reports with ATG[19]. GST, being water soluble, is rapidly absorbed after intramuscular injection, and reaches peak plasma concentrations between 2 and 6 hours after injection[2,3]. ATG is absorbed more slowly, and lower peak gold concentrations are obtained. There is a single case report of nitritoid reactions occurring repeatedly in a 41-year-old woman given auranofin[20]. She had experienced nitritoid reactions with GST given even at very low dosage (5 mg). Reactions subsided when GST was discontinued, recurred with auranofin 4–12 hours after a dose, subsided with discontinuation of auranofin, and recurred when auranofin was reintroduced. She chose to continue auranofin in spite of reactions, because of improvements in her arthritis. These reports imply a pharmacological effect of the gold itself in susceptible individuals, with the slower absorption of ATG being responsible for rarity of reactions with this formulation[1].

While the majority of nitritoid reactions are benign, serious complications can occur. The vasomotor reaction is characterized by hypotension, and the severity of the reaction depends on the degree of hypotension, the duration of hypotension, and the susceptibility of the patient to hypotensive episodes. Myocardial infarction, stroke, and transient ischemic attacks have been described associated with typical nitritoid reactions[3-7,21].

Ching and McClintock postulate that ACE inhibition

may unmask a drug hypersensitivity reaction, possibly by potentiation of kinins[18]. A similar mechanism is suggested to explain episodes of bee sting – induced angioedema occurring in individuals taking ACE inhibitors who have no history of bee sting allergy, and hypotensive transfusion reactions in patients taking ACE inhibitors[22]. ACE inhibitors prevent bradykinin breakdown; thus patients receiving ACE inhibitors are exposed to higher bradykinin levels. Particular caution should be taken in RA patients with coexisting atherosclerotic heart and peripheral vascular disease, who are more susceptible to organ damage in the event of vasodilation and hypotension.

Based on our literature review and review of our own cases over the last 4 years, we have become more vigilant, and have developed a protocol that permits recognition and management of nitritoid reactions. Unlike the majority of gold reactions, it appears that nitritoid reactions can occur at any stage of GST therapy. Usually, reactions occur within minutes after drug administration, but occasionally they can occur as long as 20 minutes after gold injection. If the reaction occurs late, it may not be observed, and the patient may not relate the symptoms to a gold injection.

Our 8 cases illustrate an apparent relationship between nitritoid reactions and a history of mucocutaneous reactions. Two of 8 were taking ACE inhibitors, a convincing association based on the literature review. None were taking ATG. Our recommendations for management include high index of suspicion when patients report flushing, nausea, or lightheadedness after a gold injection. In such patients, we recommend switching to ATG, and reduction in dose by 50% initially, injection in the recumbent position, and observation for 20 minutes after the next injection. Patients with RA taking ACE inhibitors should preferentially be given ATG. If ATG is not available, we recommend reduction of the gold dose by 50%, injection in recumbent position, and observation for 20 minutes following the next few injections. It is our experience that nitritoid reactions with GST are dose dependent, become milder, and disappear with continued gold therapy. Ordinarily, nitritoid reactions normally should not lead to discontinuation of gold therapy.

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