

Systemic Lupus Erythematosus (SLE) Induced by Quinidine

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• Only two definite cases of quinidine-induced systemic lupus erythematosus (SLE) are reported in the English-language literature. We have treated five patients who had an SLE-like syndrome while receiving quinidine. Symptoms, signs, and abnormal laboratory values improved after quinidine therapy was discontinued and prednisone therapy was started. The disease did not return after steroids were withdrawn. These cases indicate that quinidine can indeed cause an SLE-like syndrome.

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Many commonly administered cardiovascular drugs, including procainamide hydrochloride, hydralazine hydrochloride, and phenytoin sodium, can induce antinuclear antibodies (ANAs) and, occasionally, a syndrome resembling systemic lupus erythematosus (SLE).¹ Quinidine, however, is not listed in most tables of therapeutic agents implicated in provoking SLE. We know of only two reported cases in the English-language literature of quinidine-induced SLE.^{2,3} In this study, we describe five patients who had drug-induced SLE while receiving quinidine. Coagulation abnormalities, including thrombocytopenia, prolonged prothrombin (PT) and partial thromboplastin (PTT) times, and a factor IX (Christmas factor) deficiency developed in one patient.

PATIENTS AND METHODS

Data were obtained from the records of five patients who had clinical and laboratory evidence of SLE while receiving quinidine. Four of the patients were seen at the Ochsner Foundation Hospital, New Orleans, and one (patient 3) was seen at Louisiana State University Medical Center, New Orleans. The patient records were reviewed to determine the quinidine preparation used, the duration of quinidine administration before the development of symptoms, presenting symptoms and laboratory abnormalities, response to therapy, and follow-up. These data are in Tables 1 and 2. An illustrative report is provided below of one of the cases (case 1) with quinidine-induced SLE, including extra-articular disease and coagulation abnormalities.

REPORT OF A CASE

A 50-year-old man was seen at the Ochsner Foundation Hospital with a one-day history of severe bilateral pleuritic chest pain and a one-year history of severe proximal interphalangeal arthralgias in both hands, with occasional pains in other joints. He had taken several anti-inflammatory medications in the past and was receiving a combination of choline and magnesium trisilicylates, 1,500 mg, twice daily. He had been receiving 300 mg of quinidine sulfate four times daily for 18 months for a ventricular arrhythmia that was diagnosed at another hospital.

Physical examination showed an oral temperature of 37.9 °C, a systolic heart murmur, decreased bibasilar breath sounds with bibasilar dullness to percussion, and hepatosplenomegaly.

Preliminary laboratory studies showed the following values: WBCs, 7,700/cu mm, without a left shift; hemoglobin, 11.8 g/dL; hematocrit, 36.3%, with normal indexes; normal electrolyte levels; blood urea nitrogen, 19 mg/dL; creatinine, 1.9 mg/dL; glucose, 109 mg/dL; PT, 18.6 s patient/10.7 s control; PTT, 49.2 s

patient/34.2 s control; platelets, 77,000/cu mm; ESR (Westergren), 73 mm/hr; and reticulocytes, 3.9%. Arterial blood gases on room air showed a pH of 7.42, Pco₂ of 39 mm Hg, and Po₂ of 65 mm Hg; on 2 L of oxygen by nasal cannula the pH was 7.45, Pco₂ was 34 mm Hg, and the Po₂ was 96 mm Hg. The ECG was normal, and the chest roentgenogram showed bilateral pleural effusions that proved to be inflammatory and sterile after pleural fluid was obtained by thoracentesis. Ventilation-perfusion pulmonary scan was not suggestive of pulmonary embolism; a liver-spleen scan confirmed hepatosplenomegaly.

Additional laboratory studies revealed a creatinine clearance of 79 mL/min with normal urinary sediment. Iron levels of 30 µg/dL with a total iron binding capacity of 292 µg/dL were consistent with iron deficiency anemia. Complement studies showed a C3 of 170 mg/dL (normal, 115 to 260 mg/dL) and C4 of 18 mg/dL (normal, 20 to 50 mg/dL). Clotting factor assays showed factor II to be 78% (normal, 50% to 150%), factor VIII more than 100%, and factor IX was decreased at 30%. The patient's ANA was speckled and nucleolar at a titer of 1/1,024 using rat liver substrate (normal, 1/16), antibodies to double-stranded DNA and to histones were negative, as were antibodies to SS-A, SS-B, RNP, Scl-70, and SmAg. The patient's blood was negative for lupus type and for circulating anticoagulants.

Quinidine therapy was discontinued; prednisone therapy was started at 60 mg/day. Recordings of 24-hour Holter ECG monitoring showed less ventricular ectopy after this drug was stopped than recordings obtained during therapy with quinidine. Although the patient's symptoms and laboratory abnormalities (elevated ESR, thrombocytopenia, prolonged PT and PTT, and factor IX deficiency) all responded rapidly to quinidine withdrawal and steroid administration, the ANA value dropped slowly. Steroids were gradually discontinued over a three-month period. When steroids were no longer being given, symptoms and laboratory abnormalities did not return, although the patient had transient arthralgias for six months. Six months after steroids were stopped, the ANA was positive at 1/128, and one year after steroid withdrawal the ANA was 1/32. The patient has had no further problems with arthralgias, pleuritis, or high-grade ventricular ectopy.

COMMENT

Quinidine is a type I antiarrhythmic drug that is useful for atrial and ventricular arrhythmias. Toxic reactions and troublesome side effects occur in about 40% of patients receiving quinidine therapy. The most important side effects are cardiovascular and include orthostatic hypotension, increases in ventricular ectopic activity, asystole, syncope, acceleration in ventricular rate, and impaired left ventricular contractility. The most common side effect of quinidine is gastrointestinal, especially diarrhea, although anorexia, nausea, and vomiting are occasionally seen. Other side effects include cinchonism, tinnitus, visual blurring, confusion, low-grade fevers, cholestatic hepatitis, a lymphomalike syndrome, and multiple coagulopathies and blood dyscrasias.⁴

Many cardiovascular drugs, including procainamide, hydralazine, and phenytoin, induce a syndrome resembling SLE,¹ but quinidine is not listed in most tables of therapeutic agents implicated in provoking a lupuslike syndrome. In fact, we know of only three published cases in the English-language literature of SLE occurring in patients receiving quinidine,^{2,3,5} although other reports are published in another language. The 1983 *Physicians' Desk Reference* contains no mention of an SLE-like syndrome for quinidine sulfate or quinidine polygalacturonate, but under quinidine gluconate it says, "Although extremely rare, there have been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has

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Table 1.—Initial Presentation of Five Patients Who Had Drug-Induced Systemic Lupus Erythematosus While Receiving Quinidine

Patient/Age, yr/Sex, Race	Drug, Dosage, Duration*	Predominant Symptom	ESR, mm/hr	Antinuclear Antibody (ANA) Titer (Rat Liver Substrate, Normal = 1/16)	Anti-DS-DNA	Antibodies to Histones	Antibodies to SS-A, SS-B, RNP, Scl-70, SmAg
1/50/M/W	Quinidine sulfate, 300 mg QID, 18 mo	Pleuritis and polyarthralgias	73	1/1,024 speckled and nucleolar	Negative	Negative	Negative
2/71/M/W	Quinidine gluconate, 324 mg TID, 18 mo	Polyarthritits	30	1/128 homogeneous	Negative	Not tested	Not tested
3/63/F/W	Quinidine gluconate, 324 mg TID, 3 mo	Polyarthritits	47 (receiving steroids)	1/128 homogeneous, 3 mo later ANA became speckled	Negative	Negative	Negative
4/59/M/W	Quinidine sulfate, 200 mg QID, 8 mo; methyl dopa, 250 mg BID, 60 mo	Polyarthritits and peripheral neuropathy	93	1/1,024 speckled and nucleolar	Negative	Not tested	Not tested
5/74/M/W	Procainamide hydrochloride SR, 250 mg QID, 5 mo	Polyarthralgias	56	1/512 homogeneous, 6 mo later ANA was 1/64	Negative	Not tested	Not tested
	Quinidine polygalacturonate, 412.5 mg QID, 9 mo	Polyarthralgias	50	1/1,024 speckled	Negative	Negative	Negative

*QID indicates four times daily; TID, three times daily; BID, twice a day; and SR, slow release.

Table 2.—Clinical Course of the Five Patients After Quinidine Therapy Was Stopped

Patient	Treatment Duration	Time Until Patient Was Asymptomatic, mo	Repeated ESR	Repeated Antinuclear Antibody Test	Asymptomatic Follow-up	Holter ECG Monitoring Off Quinidine	Antiarrhythmic Drugs Required
1	Prednisone 60 mg/day tapered over 3 mo	6	10 (1 mo later)	1/32 (1 yr later)	18 mo	Less ventricular ectopy	None
2	Prednisone 15 mg/day tapered over 6 wk	1	12 (1 mo later)	1/16 (1 mo later)	3 yr	Unchanged	None
3	Prednisone 10 mg/day tapered over 3 mo	4	8 (6 yr later)	1/32 (6 yr later)	7 yr	Ventricular tachycardia	Propranolol and phenytoin
4	Prednisone 15 mg/day tapered over 16 mo (several times steroids were stopped and restarted)	16 (most symptoms were due to neuropathy)	8 (16 mo later)	1/32 (16 mo later)	2 yr	Unchanged	None
5	Prednisone 10 mg/day tapered over 3 mo	3	5 (15 mo later)	1/32 (15 mo later)	2 yr	Unchanged	None

not been established."⁶

Kendall and Hawkins,⁵ in 1970, described a 73-year-old woman who had dermatitis, lymphadenopathy, hepatosplenomegaly, hemolytic anemia, leukopenia, thrombocytopenia, and a positive antinuclear factor after taking 1.2 g/day of quinidine for two years. The patient's disease was controlled on low-dose prednisone, but it was impossible to discontinue quinidine therapy. Therefore, one cannot be certain that this patient's SLE was induced by quinidine.

Anderson and Wanerka,² in 1972, described a 10-year-old girl who was seen with epistaxis and thrombocytopenia after receiving 200 mg of quinidine gluconate twice daily for three years. The patient also had fever, rash, hepatic involvement, pericardial friction rub, a positive direct Coombs' test, a positive LE cell preparation, and a strongly positive antinuclear factor. Although the systemic illness resolved and the LE cell preparation became negative soon

after quinidine therapy was discontinued, the antinuclear factor remained positive six years later.

Finally, Yudis and Meehan,³ in 1976, described a 49-year-old woman who had polyarthritits, leukopenia, a positive ANA test, and signs of lupus nephropathy with a positive urinary sediment, diminished creatinine clearance, and decreased serum complement after receiving 200 mg of quinidine sulfate four times daily for three months. The case is unique for two reasons. First, the ANA test became negative shortly after quinidine therapy was stopped. Also, nephropathy is unusual in cases of drug-induced SLE. Neither conversion of the ANA test to negative nor signs of nephropathy occurred in the other two published cases or in the cases presented herein.

We described five patients (four men and one woman) who had an SLE-like syndrome while receiving quinidine (Table 1). Two of the patients had been receiving quinidine sulfate,

two were receiving quinidine gluconate, and one received quinidine polygalacturonate. All five patients were seen with polyarthritides, elevated ESRs, strongly positive tests for ANAs, and negative tests for antibodies to double-stranded DNA. One of the patients also had pleuritis with inflammatory pleural effusions and coagulation abnormalities.

An undetermined ANA was found in patients taking quinidine. Most cases of drug-induced SLE have antibodies to histones with homogeneous ANA patterns and do not have antibodies to double-stranded (native) DNA.⁷ Although none of the patients had antibodies to double-stranded DNA, four of the five patients had speckled ANAs. Three of those four patients were tested and found to have no antibodies to histones or to SS-A, SS-B, RNP, Scl-70, or SMAG. Patient 5 initially had a homogeneous ANA when he was first seen with a procainamide-induced lupus. The patient became asymptomatic one month after stopping procainamide therapy and remained asymptomatic for eight months. His ANA titer dropped from 1/512 to 1/64. A lupuslike syndrome developed eight months after starting quinidine therapy, and the ANA converted to a speckled pattern at a titer of 1/1,024. Patient 3 initially had a homogeneous ANA titer that later converted to speckled and has remained speckled six years later. Because patient 4 was receiving methyldopa, which is reported to cause an SLE-like syndrome,⁸ there is no way to know whether quinidine or methyldopa caused the lupus. The case is included here, nevertheless, because the patient had been taking methyldopa for more than five years, but the syndrome developed only eight months after he began receiving quinidine. The patient also had speckled ANAs, as did three of the four other patients presented in this report.

The index case (case 1) demonstrated coagulation abnormalities that can be caused by quinidine. These include thrombocytopenia, prolonged PT and PTT, and a factor IX (Christmas factor) deficiency. Thrombocytopenia occurs in about 3% of patients receiving quinidine and is thought to be due to antibodies to platelet-quinidine complexes. Quinidine is also known to cause hypoprothrombinemia and to potentiate the anticoagulant effects of warfarin sodium.^{4,6} We are unaware of any reports in the English-language literature of quinidine prolonging the PTT or causing a factor IX deficiency, although this is described in the non-English literature.^{9,10}

Each of the five patients in this article was withdrawn from quinidine therapy and treated with tapering doses of oral prednisone (Table 2). The reason for using corticosteroids in the first patient with significant extra-articular disease manifested by pleuritis and inflammatory pleural effusions and coagulation abnormalities seems self-evident. Many patients with drug-induced lupus caused by other agents, particularly procainamide and hydralazine, improve with drug withdrawal and do not require corticosteroid therapy. The patients described herein, however, were debilitated by their polyarthritides and required more aggressive therapy than many patients with drug-induced lupus syndromes. Prednisone was started at doses of 10 to 15 mg/day in all patients except in the one patient with extra-articular disease who received 60 mg/day, and steroids were tapered over six to 12 weeks. In one patient, steroids were restarted several times during a 16-month period because of exacerbations in lower extremity pain that was actually thought to be due to peripheral neuropathy. After quinidine withdrawal and short-term steroid therapy, symptoms slowly resolved in all five patients and did not return after steroids were withdrawn. Laboratory abnormalities also improved, although low titers of ANAs remained positive in the five patients. Symptoms have not

returned in patients followed up for 1.5 to seven years.

Only one of the five patients described in this article requires antiarrhythmic therapy now. In fact, three patients had the same amount of ventricular ectopy both while receiving and not receiving quinidine. One patient had less ventricular ectopy after quinidine was stopped. It is well known that antiarrhythmic drugs, particularly quinidine, may aggravate or even induce ventricular arrhythmia.¹¹ Therapy for high-grade malignant ventricular ectopy is controversial and is being reevaluated.¹² Many patients, including some in this article, are receiving toxic antiarrhythmic agents without evidence of high-grade malignant ventricular ectopy.

We believe the cases presented show that quinidine-induced SLE, although rare, does indeed occur. Drug-induced SLE and SLE are frequently indistinguishable syndromes. None of the five patients in this report had evidence of rheumatologic disease before receiving quinidine, and symptoms and laboratory abnormalities developed only after the administration of quinidine. Finally, and perhaps most importantly, complete resolution of the SLE occurred after quinidine therapy was discontinued, although low titers of ANAs have persisted in all five patients. Whether quinidine induces the formation of ANAs de novo or merely increased titers in patients who already have low titers of ANAs was unanswered in this article. Only one patient in this series was tested for ANAs long after the syndrome had resolved. In this patient the ANA test remained positive six years later, but the patient was requiring antiarrhythmic therapy with phenytoin, which can induce ANA formation.¹ The other four patients were not followed up long enough to determine if their ANAs would disappear, but three of these patients and one patient described in the literature² had positive ANA tests more than a year after quinidine therapy was discontinued. Prospective studies are needed to determine the incidence of quinidine-induced ANA formation and a lupuslike syndrome. Also, the type of ANA associated with quinidine is yet to be determined. Long-term follow-up would be helpful to determine if ANAs completely disappear in any of the patients described herein, and to assure that disease flares never occur long after the quinidine has been stopped.

Full case reports of patients 2 through 5 are available from the authors on request.

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