Systemic lupus erythematosus during treatment with procainamide

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We describe 7 patients in whom manifestations of systemic lupus erythematosus occurred during treatment with procainamide. Five had symptoms and the other two only changes in the blood. Pericarditis was the presenting feature in four. Symptoms quickly disappeared when the drug was withdrawn, whether steroid therapy was given or not, but the LE cell phenomenon persisted for several months. Procainamide had to be continued in two patients, one of whom required steroids to suppress the symptoms.

Procainamide, widely used for treating cardiac dysrhythmias, has been found to cause the syndrome of systemic lupus erythematosus. Since Ladd (1962) first recognized the association, 68 cases have been reported. Only five examples have so far been reported in Britain (Compton-Smith and Fawcett, 1967; McDevitt and Glasgow, 1967; Atkins, 1969; Sheldon and Williams, 1970). Our experience confirms that the incidence of this syndrome and of subclinical changes in the blood during procainamide therapy is much higher than many have supposed. We describe seven cases occurring during procainamide therapy, in which there was a notably high incidence of pericarditis.

The increasing use of antidysrhythmic drugs in the management of patients with coronary artery disease makes it desirable that physicians be aware of this complication of procainamide therapy.

Patients with clinical manifestations

Case 1 Treatment with procainamide, 500 mg four times daily, was given for frequent ventricular extrasystoles after myocardial infarction. Exactly one year later the patient was taken ill with central chest pain, aggravated by breathing, together with dyspnoea and cough. Temperature was 38.8°C, and pericardial and left pleural friction rubs were heard. There was no evidence of further myocardial infarction. Numerous lupus erythematosus cells were seen in the blood preparation. Hb 12.5 g/100 ml, ESR 84 mm in one hour. Chest x-ray suggested pericardial effusion. Procainamide was stopped and treatment with prednisone, 10 mg twice daily, was begun. One

week later he was asymptomatic and the ESR had fallen to 38 mm per hour. The dosage of prednisone was gradually reduced and it was stopped after six months. Lupus erythematosus cells were again seen five months after stopping procainamide but have not been seen on two subsequent examinations.

Case 2 Five years after repair of an atrial septal defect this woman had a prolonged attack of supra-ventricular tachycardia terminated by carotid massage. She was given procainamide, 250 mg three times daily. Nine months later she developed polyarthralgia involving the knees, ankles, shoulders, wrists, metacarpophalangeal and interphalangeal joints. Some of the joints were swollen. At this time Hb and ESR were normal, no lupus erythematosus cells were present, and the sheep cell agglutination test and antistreptolysin titres were normal. A further paroxysmal tachycardia four months later was treated by direct current (DC) reversion. At this time she was complaining of an aching frontal chest pain spreading to the shoulders and neck, exacerbated by inspiration and swallowing. There were no abnormal physical signs apart from pyrexia of 38.4°C. Skiagram of the chest showed cardiac enlargement and bilateral pleural effusions. There were numerous lupus erythematosus cells in the blood preparation and ESR was 30 mm in one hour. There was no evidence of myocardial infarction. Procainamide was stopped and treatment begun with prednisone, 10 mg three times daily. There was rapid clinical improvement, but mild central chest pain persisted for several months. The ESR quickly fell and skiagram of the chest became normal. Occasional lupus cells were present two months later but not thereafter. Prednisone was stopped after three and a half months.

Case 3 Treatment with procainamide, 250 mg four times daily, was given for treatment of

TABLE I Summary of 7 patients with procainamide-induced systemic lupus erythematosus

Case No.	Age	Sex	Diagnosis	Dosage	Duration	Treatment	Persistence LE cells
1	46	M	Ventricular ectopics after myocardial infarct	2 g daily	12 mth	Steroids; procainamide stopped	5 mth
2	40	F	Paroxysmal atrial tachycardia after ASD repair	750 mg daily	9 mth	Steroids; procainamide stopped	2 mth
3	64	F	Paroxysmal ventricular tachycardia	1 g daily	39 mth	Steroids; procainamide stopped	4 mth
4	44	F	Paroxysmal atrial tachycardia; cardiomyopathy	2.25 g daily	60 mth	Steroids; procainamide stopped temporarily	9 mth +
5	52	F	After DC reversion for atrial fibrillation	750 mg daily	5 mth	Procainamide stopped	1 mth +
<i>Asymptomatic cases</i>							
6	54	F	Paroxysmal ventricular tachycardia; coronary disease	2.25 g daily	78 mth	—	—
7	45	M	Aortic regurgitation; paroxysmal nodal tachycardia	750 mg daily	42 mth	Procainamide stopped	—

paroxysmal ventricular tachycardia. After more than three years on this treatment she developed retrosternal chest pain which radiated to the neck and to the left arm. She was febrile but there was no evidence of myocardial infarction and no dysrhythmia. Hb was 10.4 g/100 ml and the ESR 55 mm in one hour. WBC 6,000 per mm³. Skiagram of the chest showed patchy consolidation in both lower lobes with bilateral pleural effusion. A pericardial rub was heard four days later and numerous lupus cells were seen in the blood preparation.

Procainamide was stopped and prednisone, 10 mg three times daily, begun. The pericardial friction disappeared and there was rapid clinical improvement. The ESR fell to 7 mm in one hour within a month, and lupus erythematosus cells disappeared after four months. The steroid therapy was then stopped.

Case 4 This woman had prolonged attacks of supraventricular tachycardia associated with congestive cardiac failure thought to be due to a primary cardiomyopathy. The attacks could be terminated by intravenous procainamide, and oral therapy was found to control their occurrence. The dosage was increased to 750 mg three times daily. There was recurrent pleurisy and congestive cardiac failure over the next five years, but the ESR remained normal and lupus erythematosus cells were not seen.

Five years after starting procainamide she was taken ill with retrosternal pain and breathlessness. A loud pericardial rub was heard and numerous lupus cells were demonstrated. Hb was 10.6 g/100 ml, ESR 84 mm in one hour, and WBC 4,000/mm³. Electrocardiogram showed no features of myocardial ischaemia or pericarditis. Chest x-ray showed cardiomegaly and bilateral basal shadow-

ing. Rapid clinical improvement followed withdrawal of procainamide and introduction of steroids. ESR became normal but the pericardial friction was still audible after four months. Though the ESR was only 15 mm in one hour, lupus erythematosus cells were still present nine months later. Four years later the cells were no longer present. At this time procainamide was restarted for control of intractable paroxysmal tachycardia, together with steroid therapy. Lupus erythematosus cells reappeared and there was an unexplained episode of thrombocytopenic purpura. After two more years of treatment she became very ill with congestive cardiac failure and bilateral pleural effusions. At this time she had a typical facial rash of lupus. She died after a cardiac arrest.

Necropsy confirmed the presence of a diffuse cardiomyopathy without any specific features. The pericardium was adherent. No evidence was found in any of the other organs of a connective tissue disorder.

Case 5 This woman underwent successful DC reversion of atrial fibrillation after mitral valvotomy. Procainamide, 250 mg, was then given three times daily. Five months later she complained of pain and weakness in joints of the hands and wrists together with general malaise and fatigue. The affected joints were not swollen but were painful with active and passive movement. Hb 12.8/100 ml, ESR 51 mm in one hour, WBC 6,000/mm³. Lupus cells were demonstrated in the blood and antinuclear factor was present. Procainamide was withdrawn and subjective improvement quickly followed. After 5 weeks, the cells were still present, but at three months they had disappeared.

Patients with no clinical manifestations

Case 6 This woman was treated with intravenous procainamide for paroxysmal ventricular tachycardia associated with coronary arterial insufficiency. She was maintained on oral therapy which was effective with a dosage of 750 mg three times daily. Seven years after treatment began, she was treated for pneumococcal pneumonia and lupus erythematosus cells were discovered in the blood. There were no signs or symptoms attributable to systemic lupus erythematosus, and since procainamide was the only drug which effectively controlled the dysrhythmia, treatment with it was continued. She remains asymptomatic.

Case 7 This patient of 45 had rheumatic heart disease with aortic regurgitation.

In 1966 he developed paroxysmal nodal tachycardia which was corrected by intravenous procainamide, and he was at that time started on procainamide, 250 mg t.d.s. by mouth. He remained on the drug until April 1970, when a routine lupus erythematosus phenomenon test was performed and found to be positive. He has had no symptoms or physical signs which could be attributed to systemic lupus erythematosus, and all special investigations, apart from the lupus phenomenon, have been normal.

Discussion

The features of 33 cases of procainamide-induced systemic lupus erythematosus were compared with the spontaneous variety of Dubois (1969) (Table 2). The most important difference was the absence of renal involvement in the procainamide cases. Since this is the most ominous feature of systemic lupus erythematosus, its absence may be

responsible for the notably better prognosis in the drug-induced variety. There is also a lower incidence of rash and lymphadenopathy in procainamide-induced systemic lupus erythematosus and a higher age of incidence. Except for the high incidence of pericarditis, the features of our cases correspond closely with those of Dubois.

Pericarditis was a presenting feature in four of our seven patients (57%). All four had typical chest pain, and a pericardial friction was heard in three; pericardial effusion was suspected in two of them. None, however, had characteristic electrocardiographic abnormalities. We believe that pericarditis is a particularly important feature of the syndrome. Many patients having procainamide for the control of dysrhythmia are suffering from coronary disease and may have had previous myocardial infarction, and the procainamide-induced systemic lupus erythematosus syndrome occurs at an age when coronary disease is common. There is, therefore, a real risk of diagnostic error, mistaking the pain for that of myocardial infarction. Even when it is recognized, pericarditis might wrongly be ascribed to infarction or to the post-myocardial infarction syndrome which it may closely resemble. Similarly, in other cases, it may be mistaken for the post-cardiotomy syndrome.

The other common features were pleurisy, often with effusion, and fever. Arthropathy was much less common in our cases than in previous reports. One of our patients had a typical facial rash – an unusual finding in drug-induced systemic lupus erythematosus.

TABLE 2 Manifestations of systemic lupus erythematosus

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Average incidence	Average in procainamide systemic lupus erythematosus (Dubois)	Average in idiopathic systemic lupus erythematosus (Dubois)
Age (yr)	47	40	68	54	53	54	46	49.3	57.5	27.5
Anorexia	—	—	+	—	+	—	—	30%	0	53.2%
Pleurisy	+	+	—	+	—	—	—	43%	51.5%	43%
Myalgia	—	—	—	—	—	—	—	0	27.2%	48.2%
Fever	+	+	+	—	—	—	—	43%	39.2%	83.6%
Rash	—	—	—	+	—	—	—	14%	18%	71.5%
Adenopathy	—	—	—	—	—	—	—	0	0	53.6%
Arthritis	—	+	—	—	+	—	—	30%	91%	91.6%
Pleural effusion	+	+	+	+	—	—	—	57%	33.3%	30.3%
Pericarditis	+	+	+	+	—	—	—	57%	18.2%	30.5%
Lupus erythematosus cells	+	+	+	+	+	+	+	100%	94%	75.7%
Anaemia (11.5 g/100 ml)	—	—	+	+	—	—	—	30%	21.3%	56.5%
Proteinuria	—	—	—	—	—	—	—	0	0	46.1%
Dysproteinemia	—	—	—	—	—	—	—	0	38.5%	53%

Symptoms appeared after procainamide had been given for between 5 and 60 months, and the two asymptomatic patients had taken the drug for 42 and 78 months when the cells were discovered. Dosage was between 750 mg and 2.25 g daily. Level of dosage and duration of treatment did not seem to be significant in determining the onset of systemic lupus erythematosus, and cases have been reported where symptoms have appeared as little as one month after starting treatment (Kaplan *et al.*, 1965).

Procainamide was stopped as soon as the diagnosis was made in six out of the seven patients. Steroid therapy was given in four for a period of months. Symptoms abated fairly quickly but steroid therapy seemed to bring about more rapid relief. Our experience suggests that, if the procainamide is stopped, steroid therapy need only be given with a diminishing dosage for a short period and need not be continued until the lupus erythematosus cells disappear.

In two patients, treatment with procainamide had to be continued or resumed in spite of the development of systemic lupus because no other form of treatment was effective. In one of them (Case 6), the illness was subclinical. It is now two years since it was recognized and no clinical manifestations have yet developed. The other (Case 4) was a more difficult problem. She had an obscure form of cardiomyopathy which was responsible for prolonged and dangerous bouts of dysrhythmia which only responded to procainamide. We carefully reviewed her history and her extensive investigations, and excluded primary systemic lupus erythematosus as the cause of the cardiomyopathy. It was necessary to resume procainamide therapy with steroid cover. This suppressed the clinical manifestations and kept her in reasonable health. The thrombocytopenic purpura which subsequently developed might have been a further expression of the disorder but could have had some other explanation. Her death from cardiac arrest during treatment for severe congestive failure was mainly the result of the cardiomyopathy, and systemic lupus erythematosus played little if any part. There have been three previous necropsy reports of patients with procainamide-induced systemic lupus erythematosus (Dubois, 1969). As in our Case 4 no characteristic histological features were found.

Drug-induced lupus erythematosus has recently been reviewed by Alarcón-Segovia (1969). He believes that there are two ways in which it develops (Table 3). Firstly there are drugs which produce it because of their

peculiar chemical structure, and secondly those with which the disease develops as an allergic phenomenon in association with other allergic manifestations. Procainamide is in the

TABLE 3 *Drugs inducing systemic lupus erythematosus* (after Alarcón-Segovia)

<i>Drugs thought to act because of pharmacological structure</i>	<i>Drugs thought to act by sensitivity phenomenon</i>	
Hydrallazine	Penicillin	Methylthiouracil
Isoniazid	Tetracycline	Propylthiouracil
Phenytoin	Sulphonamides	Reserpine
Methoin	Amino salicylic acid	Methyldopa
Troxidone	Griseofulvin	Oral contraceptives
Primidone	Phenylbutazone	Guanoxan
Procainamide		

first group along with hydrallazine; in these, prolonged exposure to the drug is necessary. The genetically determined rate of acetylation of the drug in the liver may play some part.

We have no data to indicate exactly how many patients had long-term therapy with procainamide during the period that our seven cases came to light, but our impression is that the risk of developing the complication is high among those taking the drug for longer than three months.

Dubois (1969) studied 22 patients who had taken procainamide for six weeks or longer. None had symptoms of lupus erythematosus but 17 of them (77%) had serological changes. Twelve of the 22 had lupus cells, 15 had anti-nuclear antibodies, and 8 had antibodies to DNA. Thus the serological manifestations occur very frequently. Our experience suggests that some patients with positive serology will not develop clinical manifestations for a very long time, if at all, but many, probably the majority, do.

Systemic lupus erythematosus is a common complication of treatment with procainamide. It should always be considered in the diagnosis of inter-current illness in patients who are taking the drug, particularly if there is pericarditis, pleurisy, or arthritis. It can be managed safely with the help of steroids, and the drug may, if necessary, be continued. The especial danger of this form of systemic lupus erythematosus lies in failure to recognize it and identify its cause.

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