Procainamide-induced systemic lupus erythematosus

P. J. H. S. SHELDON AND W. R. WILLIAMS*

Department of Rheumatology and Physical Medicine, Middlesex Hospital, London

Ladd (1962) described the case of a 49-year-old man who was taking procainamide 1 to 2 g. daily. In the space of 3 months he developed a rash, migrating arthralgia, and pleuritic chest pain. LE-cells and antinuclear factor were present, but disappeared along with the rash and arthralgia within 9 weeks of discontinuing the drug.

This case drew attention to the role of procainamide in inducing a condition resembling systemic lupus erythematosus (SLE). Other drugs implicated include hydralazine, mephenytoin, diphenylhydantoin, troxidone, streptomycin, isoniazid, penicillin, tetracycline, sulphamethoxypyridazine, sulphadimethoxine, griseofulvin, reserpine, and thiouracils (Lee, Rivero, and Siegel, 1966), and more recently oral contraceptives (Schleicher, 1968; Bole, Friedlaender, and Smith, 1969).

Only three reports of procainamide-induced SLE have appeared in the British literature (Compton-Smith and Fawcett 1967; McDevitt and Glasgow, 1967; Atkins, 1969).

This paper describes two further patients with this syndrome, who were seen at the Department of Rheumatology and Physical Medicine of the Middlesex Hospital.

Material and methods

L.E.-cells were demonstrated by the method of Zinkham and Conley (1956).

Antinuclear factor (ANF) titre was estimated by the method of Roitt and Doniach (1966).

Anti-IgG levels were estimated by the method of Torrigiani and Roitt (1967).

Case Reports

(1) A male European aged 61 years (Table I and Case 54 in Table III) was admitted to another hospital in May, 1968, on account of a cardiac arrhythmia and angina. Whilst there he was given procainamide 0.75 g. daily. After 7 months he developed arthralgia of the hands, shoulders, and knees, and pleuritic pain.

He was admitted to the Middlesex Hospital in January, 1969, where he was noted to be in congestive cardiac failure. There was pain on movement of the wrists, and inflammation of several metacarpophalangeal joints. Investigations showed a raised erythrocyte sedimentation rate, leucopenia, a positive L.E.-cell test, and antinuclear factor.

The congestive cardiac failure was treated by digoxin 0.25 mg. twice daily and frusemide 40 mg. once daily, and procainamide was discontinued. The joint symptoms resolved within 72 hours, but L.E.-cells were still present 5 weeks later, when the patient left for Australia.

Table I *Investigations of Case 1 (Case 54 in Table III)*

Date	WCC (cells/cu. mm.)	Erythrocyte sedimentation rate (mm./1 hr) (Westergren)	L.E.-cells	Antinuclear factor titre
10 March, 1969	3,600	73	+	1 : 1,280
11 March, 1969	Procainamide discontinued			
28 March 1969	5,600	51	+	
15 April 1969		20	+	1 : 320

* Present address Medical Registrar, North Middlesex Hospital, London, N.18.

Table II Investigations of Case 2 (Case 55 in Table III)

Date	WCC (cells/cu. mm.)	Erythrocyte sedimentation rate (mm./1 hr) (Westergren)	L.E.-cells	Antinuclear factor titre	Anti IgG (µg./ml.)
27 January 1969	7,100	60		1 : 5,120	
11 March, 1969		63			
23 March, 1969	4,400	70	+		168
8 April, 1969	Procainamide discontinued				
11 April, 1969		43	+	1 : 320	110
22 April, 1969	3,400	65	+	1 : 320	142
15 May, 1969	3,800	55	+	1 : 2,560	46
2 February, 1970				1 : 320	
4 March, 1970			—		

(2) A male European aged 67 years (Table II and Case 55 in Table III) gave a history of 'nephritis' 18 years previously. In May, 1968, he was admitted to the Middlesex Hospital with a cardiac infarction, confirmed by electrocardiogram. Ventricular tachycardia ensued and was successfully treated by a lignocaine infusion, after which he was given oral procainamide 1 g. gaily. After 5 months he developed arthralgia, involving the wrists, elbows, shoulders, and knees, with considerable weakness, malaise, and loss of weight.

He was re-admitted in January, 1969. There was no joint swelling, but generalized stiffness, weakness of grip, and inability fully to extend the left elbow on account of pain. The other systems were essentially normal. Investigations showed a raised erythrocyte sedimentation rate, leucopenia, positive L.E.-cell test, and antinuclear factor in high titre.

Procainamide was tailed off over a period of 10 days, and a week later the patient felt better, the arthralgia subsided, and the grip became stronger, but some malaise and stiffness persisted. Antinuclear factor was still demonstrated in high titre 10 months later. L.E.-cells were absent 11 months after the discontinuation of procainamide.

Discussion

The total number of instances in which procainamide has hitherto been reported to cause SLE is 65 (Lappat and Cawein, 1968; Mehta, 1968; Dubois, 1969; Atkins, 1969; Byrd and Schanzer, 1969).

Details of 44 cases and of the two new patients presented above are given in Table III (overleaf).

The dosage varied from 0.5 to 6 g. daily, and the duration of therapy leading to symptoms of SLE ranged from 2 weeks to 6 years.

The predominant clinical features were malaise and migratory arthralgia, occasionally with swelling of the proximal interphalangeal joints of the fingers. Pleurisy occurred in about half the cases, and some developed pericarditis. Case 53 developed a restrictive defect with an associated impairment of gas transfer in spite of discontinuation of procainamide and the exhibition of steroids. Rashes, consisting of

a simple erythema, erythema multiforme, or purpura, have also been described.

Laboratory investigations usually showed a raised ESR and leucopenia. The L.E.-cell test was positive in all except Case 8 and Case 27, but in both these patients the history was suggestive of procainamide-induced lupus and the antinuclear factor was present. The response to the withdrawal of procainamide was dramatic, though in Case 8 steroids were given. Many patients had raised gamma globulin and antinuclear factor. The height of the antinuclear factor titre did not necessarily correlate with the severity of symptoms (Fakhro, Ritchie, and Lown, 1967). Antibody to IgG was measured in Case 55, this particular estimation not having previously been carried out. Raised levels were also found in cases of sero-negative rheumatoid arthritis, and in Still's disease (Torrighiani, Ansell, Chown, and Roitt, 1969). Renal dysfunction was relatively infrequent, only three patients showing proteinuria or a rise in blood urea. Renal biopsy was carried out only in Case 43, and the findings were normal. Bone marrow examination in Cases 5 and 8 showed plasmacytosis.

Treatment in all cases of procainamide-induced lupus consisted of withdrawal of the drug once its action was appreciated, though the rapidity with which this was done was tempered by other clinical considerations. Steroids were prescribed, with benefit, in nearly half the cases.

From the foregoing it is evident that an immune response to procainamide is evoked in certain patients. Why some but not all should be affected is not clear, but genetic factors may be implicated. In the case of spontaneous lupus erythematosus, a familial incidence has been reported (Peterson and Good, 1963). It is recognized that there is frequently a well-substantiated family history of rheumatic disease in these patients (Holley, 1964). These findings have been interpreted as indicating that such individuals possess an immunological handicap probably genetic in origin, which may antedate the

Table III *Clinical particulars of 46 patients out of 55 cases reported*

Case no.	Authors	Date	Sex	Age (yrs)	Daily dose (g.)	White cell count (cells/cu. mm.)	ESR	L.E.-cells	Antinuclear factor titre
1	Ladd	1962	M	49	1-2	8,500		+	1 : 8
2	Hahn	1964	M	65	<4	3,000	22	+	
3			F	49	1			+	
4	Colman and Sturgill	1965	F	40	2	3,900	72	+	1 : 4,096
5	Kaplan, Wachtel, Czarnecki, and Sampson	1965	F	47	1.5-2	3,750	53	+	+
6			F	53	3	7,300	27	+	+
7			F	70	0.75-2	10,500	54	+	
8			F	51	2	7,100		-	++
9	Paine	1965	M	59	1.5		15	+	
10			F	65	2			+	
11			M	63	1			+	
12			F	72	0.5	3,810		+	
13	Prockop	1966	F	36	2-5			+	+
14	London and Pincus	1966	M	50	1.5	6,400	22	+	
15			F	53				+	
16	Sanford, Michaelson, and Halpern	1967	F	69	0.75-1			+	
17			M	74	0.75-2			+	
18	Hanlon, Binkiewicz, Feingold, and Necheles	1967	F	4	<4	3,000	116	+	1 : 64
19	Rosin	1967	M	53	2			+	
20	Compton-Smith and Fawcett	1967	M	70	1-2	5,600	49	+	
21	McDevitt and Glasgow	1967	F	50	2		70	+	+
22	Fakhro, Ritchie, and Lown	1967	M	41	4				1 : 64
23-25			(3)*						
26			M	66	1-2			+	1 : 1,024
27			F	63	<6			-	1 : 32
28			M	61	0.75-2			+	1 : 32,768
29-30			(2)*						
31			F	68	1			+	1 : 64
32			M	59	1			+	+
33-36			(4)*						
37	Carabia and Fortney	1965	F	50	1-2	5,200		+	

* Individual details of these nine cases mentioned by Fakhro and others (1967) not supplied.

<i>Proteinuria</i>	<i>Pleurisy</i>	<i>Duration to start of symptoms (mths)</i>	<i>Duration to stopping drug (mths)</i>	<i>Interval from start of symptoms to stopping drug (mths)</i>	<i>Interval from stopping drug to negative L.E.-cell test (mths)</i>	<i>Steroids given</i>
+	+	3	3	0	2½	No
	+	3/4	18	17		Yes
		2			1	No
—	+	4	4	0		No
	+	9	11	2		No
—	+	3	3	0		Yes
—	+	5	10	5	25	Yes
—	—	1	12	11	ANF negative after 5 mths	Yes
	+	4	4	0	3	Yes
		2	8	6	8	No
		7	9	2		No
	+	22	60	38		No
		19	19	0		Yes
—		15	28	13	7	No
		1				No
	+	2½	26	24	6	Yes
	+	11	13	2		Yes
	—	12	12	0		No
—	—	c.1	c.1	0		Yes
—	+	8	13	5		Yes
	+	4	5	1	1½	No
	—					No
	+					
	—	6	9	3		No
		>3	36			No
	—	15	15	0		No
	+	10	10	0	3	No
	+	72	72	0		Yes
	—	4	4	0	1½	No

continued

Table I continued.

Case no.	Authors	Date	Sex	Age (yrs)	Daily dose (g.)	White cell count (cells/cu. mm.)	ESR	L.E.-cells	Antinuclear factor titre
38	Oster	1966	M	56		2,300		+	
39	Hunt	1968	M	77	<1		43	+	
40	Skipworth, Morris and Goldstein	1967	M	53				+	
41	Rutherford	1968	F	55	2		51	+	
42			F	72	2	3,800	8	+	
43			F	75	0.75	4,600	76	+	
44	Lappat and Cawein	1968	F	51	2	3,600	30	+	1 : 100
45	Mehta	1968	M	45	1			+	—
46	Dubois	1969	M	69	1	3,500	23	+	
47			M	72	2		51	+	+
48			F	77	1-2		47	+	
49			M	68				+	
50			M	64	6	3,800	27	+	+
51			M	61	1	3,700		+	
52	Atkins	1969	F	55	0.5-0.75	5,300	46	+	1 : 250
53	Byrd and Schanzer	1969	M	35	0.75			+	+
54	Sheldon and Williams	1970	M	61	0.75	3,600	73	+	1 : 1,280
55			M	67	1	3,400	70	+	1 : 5,120

disease by many years and may manifest itself by any of the rheumatic diseases, particularly SLE. These people possess the so-called 'lupus diathesis', *i.e.* they have some underlying idiosyncrasy that may result in an abnormal immunological reaction to a noxious stimulus—whether an infection or a drug. The family of one patient with procainamide-induced SLE (Case 44) has been investigated immunologically (Lappat and Cawein, 1968); of eight relatives studied one had L.E.-cells, and three had demonstrable antinuclear factor. The development of antinuclear antibodies in asymptomatic patients taking procainamide has been reported (Fahkro and others, 1967; Dubois, Molina, Bilitch, and Friou, 1968; Blomgren, Condemi, Bignall, and Vaughan, 1969).

Why are these abnormal antibodies produced? It may be that in certain genetically predisposed individuals various drugs alter normal circulating antibody rendering it antigenic. The similarity of structure of procainamide to that of various other drugs also implicated in causing lupus erythematosus

is evident from the Figure. Similar chemical moieties may act as inducing agents, initiating the production of antigen, possibly by hapten formation (Rosin, 1967). Natural procainamide antibody was reported in 30 per cent. of normal subjects using procainamide amide-tagged sheep red cells (Russell and Ziff, 1968), whereas in patients with procainamide-induced SLE only 6 per cent. had antibody. This has been interpreted as showing that the antibody may be undergoing absorption from the serum either in the form of potentially harmful circulating complexes with procainamide or by direct reaction with sub-cellular tissue components released during the course of the disease.

Conclusion

The aetiology of SLE is unknown. The spontaneous, or non-drug-induced type, is usually more serious with a greater tendency to involve the kidney. Psychoses and neurological abnormalities quite commonly occur. The patients are usually females

Proteinuria	Pleurisy	Duration to start of symptoms (mths)	Duration to stopping drug (mths)	Interval from start of symptoms to stopping drug (mths)	Interval from stopping drug to negative L.E.-cell test (mths)	Steroids given
—	—	1				Yes
—	—					Yes
+	+	25	66	41		No
+	+	11	11	0		Yes
+	—	$\frac{1}{2}$	$\frac{1}{2}$	0	1	No
—	+	21	103	82		Yes
—	—	5	5	0		Yes
—	—	25				Yes
—	+	15	19	4		Yes
—	+	8				No
—	—	20			Still + after 2 yrs	Yes
—	—	9	10	1	Still + after 4 mths	No
—	—	9	11	2	4	No
—	—	55			Still + 12 mths later	No
—	—	3	6	3	1	No
—	+	35	43	8	2 $\frac{1}{2}$	Yes
—	+	8	10	2		No
—	+	5	6	1	— at 11 months	No

FIGURE.

of child-bearing age. In contradistinction procainamide-induced SLE tends to affect older people (median age 60 years), and the sex incidence is approximately equal. It is usually more benign in its course and generally responds to withdrawal of the drug, though the speed of response is not always

as rapid as earlier reports would suggest and evidence of an immune process may remain for several years after the drug has been discontinued (Dubois, 1969). Steroids probably accelerate clinical improvement. Patients developing drug-induced SLE may possess an underlying lupus diathesis, the combined effect of this immunological handicap plus long-term drug administration resulting in the appearance of a benign form of SLE.

The syndrome may be far more common than hitherto appreciated, and will doubtless be diagnosed more frequently in the future. It is suggested that patients who develop arthralgia, rashes, or pleuritic symptoms whilst taking procainamide be further investigated to exclude the presence of a potentially reversible drug-induced SLE syndrome.

Summary

Two cases of procainamide-induced systemic lupus erythematosus are presented, and 44 out of 65 cases

previously reported between 1962 and 1969 are reviewed. The possible role of procainamide in the induction of SLE is discussed, and it is suggested that this condition is likely to be far more common than hitherto recognized.

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RÉSUMÉ

Le lupus érythémateux disséminé provoqué par la procainamide

Deux cas de lupus érythémateux disséminé provoqués par la procainamide sont présentés et 44 des 65 cas rapportés précédemment entre 1962 et 1969 sont passés en revue. Le rôle probable de la procainamide dans l'induction du lupus érythémateux disséminé est discuté, et il est suggéré qu'il est probable que cette affection soit plus commune qu'on ne l'avait pensé jusqu'ici.

SUMARIO

Lupus eritematoso diseminado inducido con procainamida

Se presentan dos casos de lupus eritematoso diseminado (LE) inducidos con procainamida y se analizan 44 de 65 casos mencionados anteriormente entre 1962 y 1969. Se discute el posible papel de la procainamida en la inducción del LE, y se sugiere que esta condición quizá sea mucho más común de lo que se ha admitido hasta ahora.